Communicating risk effectively

Piening, Sigrid

Communicating Risk Effectively

This study was funded by an unconditional grant from the Dutch Medicines Evaluation Board (CBG-MEB).

Printing of this thesis was partially supported by the University of Groningen, the Graduate School for Health Services Research (SHARE), and the University Medical Center Groningen.

Additional financial support for the printing of this thesis was received from the CBG-MEB and the Nederlands Bijwerkingen Fonds.

ISBN: 978-90-367-6441-4 (printed version)

ISBN: 978-90-367-6440-7 (digital version)

Lay-out: Sigrid Piening

Cover-design: Sigrid Piening & Doran Schmaal

Printed by: GVO drukkers & vormgevers B.V. | Ponsen & Looijen

RIJKSUNIVERSITEIT GRONINGEN

COMMUNICATING RISK EFFECTIVELY

Proefschrift

ter verkrijging van het doctoraat in de
Medische Wetenschappen
aan de Rijksuniversiteit Groningen
op gezag van de
Rector Magnificus, dr. E. Sterken,
in het openbaar te verdedigen op
woensdag 2 oktober 2013
om 12.45 uur

door

Sigrid Piening

geboren op 31 maart 1983
te Noordbroek

Promotores:	Prof. dr. F.M. Haaijer-Ruskamp Prof. dr. P.A. de Graeff
Copromotores:	Dr. P.G.M. Mol Dr. S.M.J.M. Straus
Beoordelingscommissie:	Prof. dr. H.G. Leufkens Prof. dr. R.E. Löfstedt Prof. dr. B.H. Stricker

Paranimfen: Edwin van Adrichem
Marije van Leeuwen

Table of contents

Chapter 1

Introduction

When a drug is allowed to enter the market, a long period of research has come to an end which is bound to strict rules to ensure a positive benefit/risk balance of the drug. Not only do drugs have many benefits, they also carry risks that can cause hospitalization, disablement, or even death of patients.[1-4] In their development phase, drugs are tested in small groups of relatively healthy people, often for a short period of time.[5] While after marketing approval, drugs are often used long term, by an older population that is frequently using other medication related to pre-existing diseases.[6,7] Also, pre-marketing clinical trials are primarily aimed at establishing the efficacy of drugs and not their safety. This means that only the most common side effects are known at market entry, causing the benefit-risk profile of a drug to be incomplete. Consequently the safety of a drug needs to be monitored after market approval. This protective activity is called pharmacovigilance. The World Health Organisation defines pharmacovigilance as follows:

'[…] *the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems.*'[8]

The European Medicines Agency, the Dutch Medicines Agency, and the Dutch Health Care Inspectorate are the responsible authorities at European and Dutch level respectively.

Safety-related regulatory action

An important component of pharmacovigilance is risk communication of serious safety issues of drugs after market approval. Healthcare professionals need to be informed when serious safety issues emerge, to ensure safe and effective use of medicinal products.[9] In the European Union this is done mainly by sending paper-based warning letters to healthcare professionals, so called Direct Healthcare Professional Communications (DHPCs). A DHPC is sent by the responsible marketing authorisation holder at the instigation of the European Medicines Agency and/or the national authority. The content of a DHPC must conform to a fixed template and can be issued in case of:[10]

- *suspension, withdrawal or revocation of a drug;*
- *an important modification of the product information;*
- *limited availability;*
- *a change in the benefit/risk balance;*
- *new recommendations for treating or preventing adverse reactions;*
- *on-going assessment of an important potential risk, with insufficient existing data to take regulatory action.*

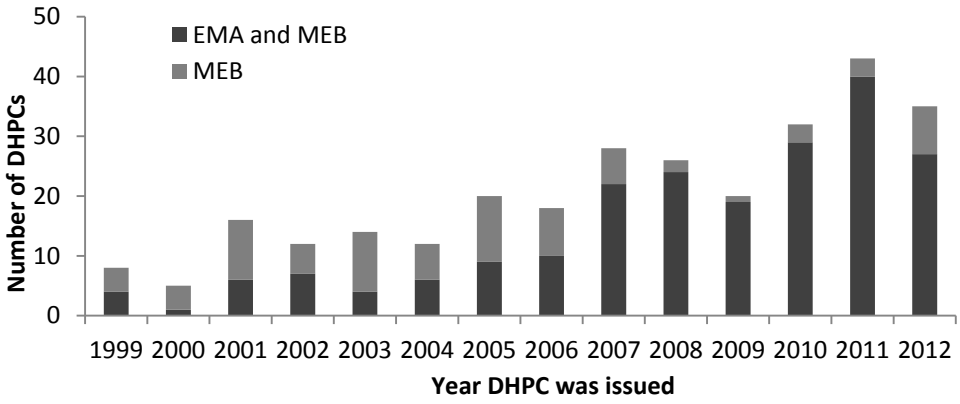

Figure 1. DHPCs issued in the Netherlands (1999-2012).
The DHPCs were issued by the pharmaceutical company at the instigation of the European Medicines Agency (EMA) and/or the Dutch Medicines Evaluation Board (MEB).

Scope of the problem

Between January 1999 and January 2013 289 DHPCs were issued for 190 different active substances[11] encompassing 14,8% of the total number of unique active substances that were available on the Dutch market (**Figure 1**).[12]

The DHPCs were issued for a wide range of drugs and safety issues. The three most frequent Anatomical Therapeutic Chemical drug classes were: anti-neoplastic and immunomodulating agents (22%), anti-infectives for systemic use (15%), and alimentary tract and metabolism (14%). For the DHPCs that were issued from 1999 to 2009 the safety issues mainly concerned cardiac disorders (15%), injury, poisoning and procedural complications (13%), and general disorders and administration site conditions (10%).[11] Relatively few DHPCs concerned a withdrawal of the drug from the market,[11,13] but these cases often received a great deal of media attention. For example, the cases of rofecoxib (Vioxx®) in 2004 and rosiglitazone (Avandia®) in 2010 were extensively discussed in lay and professional media. DHPCs were issued during the whole lifecycle of drugs with 26% being issued 10 years or more after registration (**Figure 2**). The median time between registration and the first DHPC was 5 years (ranging from 0 to 48 years). The number of warning letters that is issued increases by 2.4 DHPCs per year.

The effectiveness of drug safety warnings is questioned.[14,16] In some cases repeated warnings were still not sufficiently complied with, resulting in the drug being taken off the market, since its safe use could not be guaranteed any longer.

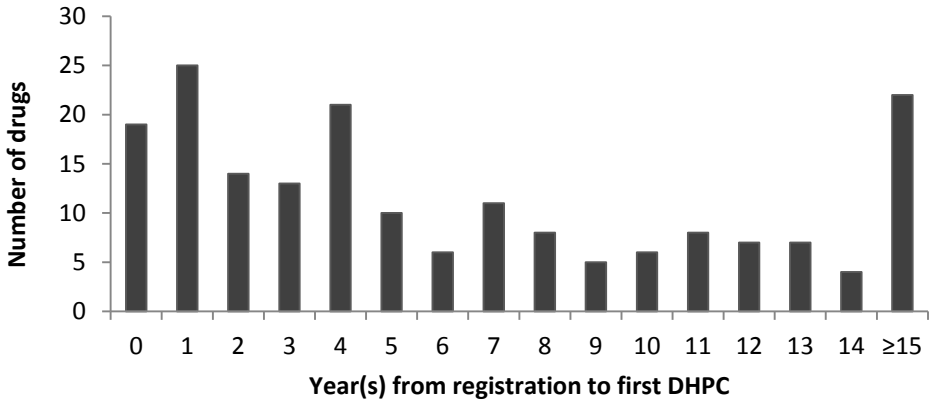

Figure 2. Time from registration to first DHPC (1999-2012)

For example, in the United States five consecutive DHPCs (1995-2000) were issued to warn healthcare professionals about cardiovascular problems related to the use of cisapride (Prepulsid®). Prescribing of cisapride with contra-indicated medications continued, eventually leading to its market withdrawal in 2000.[17,18]

Also unintended effects can occur due to safety warnings.[19] In 1995, the United Kingdom venous thromboembolism DHPC for third generation oral contraception generated a pill scare. It caused many women to cease use of oral contraceptives all together, resulting in an increasing number of conceptions and abortions.[20-22] The selective serotonin reuptake inhibitor (SSRI) warnings that were issued between 2003 and 2006 recommended to reduce prescribing of SSRIs to the adolescent population only, due to a risk of suicidality and suicidal thoughts.[23,24] Unintended decreases in adult SSRI prescriptions were observed, possibly associated with an increased number of suicides.[25-27]

The opinion about the impact of safety warnings is largely based on these and similar high profile safety cases. Little is known about the impact of DHPCs that were less extensively discussed in the media as well as the experiences and preferences of healthcare professionals regarding the DHPCs, especially in the Dutch setting. Such knowledge is vital to enable optimization of current risk communication methods. Effective risk communication is at the heart of successful risk management.[28] Moreover, in July 2012, new pharmacovigilance legislation is implemented which made evaluation of the effectiveness of risk minimization measures mandatory.[29,30] A point of reference regarding the effectiveness of DHPCs can be established. Interventions as well as policy

changes that are based on the preferences of healthcare professionals will increase their chance of success. And, above all, patient safety can be improved.

Communicating risk effectively

Over the last decades, people have become more concerned about risks,[31] leading to increased risk communication efforts. Risk communication can have different aims; to share information, change beliefs, or change behaviour. Changing specific behaviour such as drug prescribing is not always intended, sometimes the aim is merely to inform or educate. To date, it is no longer sufficient to present the public with quantitative risk estimates,[32] which only aims to share information, regardless of whether the message is understood.[19] Risk communication can be considered adequate when the information is useful to its audience[19] and this involves more than just presenting the numbers. The goal of a warning depends on each specific situation and should be linked to the desired outcome of the risk communication.[19]

The effectiveness of a warning depends on a combination of the characteristics of the target audience, the characteristics of the source of the message, as well as the content of the message.[33] Concerning the target audience, it is important to understand how they perceive risk.[34,35] In general, people have sophisticated ideas about risks.[36] Risks are not only judged analytically, feelings are involved in the decision process as well.[37-39] Slovic and colleagues called the dependency on these feelings 'the Affect Heuristic'.[38] Psychological, social and cultural aspects can influence risk perception and people give meaning to a message in a socio-cultural context.[36-40] According to Slovic, this means that *'the concept 'risk' means different things to different people'*.[41]

Not all risk perception factors play a role in each situation and the degree to which they contribute varies as well.[35] This implies that in risk communication there is 'no one size fits all'. Every single situation needs to be assessed individually, underlining the complexity of successful risk communication. With regard to the way that risks of medicines are perceived by healthcare professionals, it can be expected that trust plays an important role. The source of the information is primarily important in relation to its credibility. When trust and credibility of the source of the information are questioned, the message will not be heard, believed and acted upon.[31,34,42] Credibility is even more relevant when the receivers of the message are not highly knowledgeable of the issue at hand. This plays a clear role when considering risk communication about new drug safety issues. Pharmaceutical companies are often distrusted because of their commercial interests. This may compromise the effectiveness of DHPCs since they are disseminated by the companies.[33,36,43]

With regard to characteristics of the content of the message, the seriousness of the risk described and its consequences for the people involved are relevant. One may expect healthcare professionals to be more open to change their behaviour in case of safety issues with a high impact on patient outcome such as (irreversible) disablement or mortality. Another aspect that could influence the effectiveness of risk communication is the perceived benefit of the drug. It can be expected that higher risks will be accepted for drugs with greater benefits.[44]

In addition, it is clear that the channel that is used may also affect the response of the target audience.[19] Of course, in urgent risk communication not all methods may be equally useful or practically feasible. Nevertheless, in contrast to paper-based DHPCs various fast communication methods using IT solutions are available; e.g. internet, e-mail, social media, twitter, etcetera. Empirical evidence for preferences of the busy healthcare professional with respect to communication channels is however lacking.

Although much progress has been made in understanding what is effective risk communication, little is known about this in the area of communicating risks of medicines to healthcare professionals. With better understanding of how risk perception factors play a role in communicating serious safety issues of medicines, regulators can improve current methods, (partially) predict responses to particular cases and develop new risk communication strategies.[41,45] By doing so, it can be possible to achieve changes in attitudes as well behaviour as intended by the message.[34]

In this thesis we present the results of the Communicating Risk Effectively (CORE) study. The CORE study is designed to contribute to better risk communication of regulatory bodies by providing empirical evidence of the effectiveness of DHPCs, and the relevance of characteristics of their content, target population, and the information channel.

The aims of the CORE study are:

- To provide an overview of the impact of DHPCs and to explore determinants that influence the impact of DHPCs.
- To explore what the experiences and preferences of Dutch healthcare professionals are with regard to DHPCs.
- To determine the added value of a new risk communication method, that is based on the preferences of healthcare professionals.

Outline of this thesis

This thesis covers two parts. The first part consists of three studies that give an overview of the impact of safety-related regulatory actions.

- In **chapter 2** we reviewed the literature regarding the impact of safety-related regulatory action.
- **Chapter 3** gives an overview of the short-term and long-term impact of a large group of DHPCs on drug use.
- In **chapter 4** we assessed which determinants influence the impact of DHPCs on drug use.

The second part of this thesis consists of two studies that focus on the optimization of the impact of DHPCs.

- In **chapter 5** we present the results of a survey that was conducted to identify the experiences and opinions of Dutch healthcare professionals regarding DHPCs.
- Based on the results discussed in chapter 5, an intervention study is performed to determine the added value of a safety warning that is e-mailed to Dutch healthcare professionals. These results are shown in **chapter 6**.

Finally, in **chapter 7** the main findings as well as the implications of the CORE project are summarized and discussed. In addition, recommendations for further research and improvements of current risk communication are given.

This chapter was partly based on:
Mol, P.G.M.; Straus, S.M.J.M.; Piening, S.; De Vries, J.T.N.; De Graeff, P.A.; and Haaijer-Ruskamp, F.M. A decade of safety-related regulatory action in the Netherlands: A retrospective analysis of Direct Healthcare Professional Communications from 1999 to 2009. Drug Saf 2010; 33(6):463-474.

References

1 Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: Prospective analysis of 18 820 patients. Br Med J 2004 07;329(7456):15-19.

2 Leendertse AJ, Egberts ACG, Stoker LJ, Van Den Bemt PMLA. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. Arch Intern Med 2008 09;168(17):1890-1896.

3 Van der Hooft CS, Dieleman JP, Siemes C, Aarnoudse ALHJ, Verhamme KMC, Strieker BHCH, et al. Adverse drug reaction-related hospitalisations: A population-based cohort study. Pharmacoepidemiol Drug Saf 2008 17(4):365-371.

4 Schneeweiss S, Hasford J, Gottler M, Hoffmann A, Riethling A-, Avorn J. Admissions caused by adverse drug events to internal medicine and emergency departments in hospitals: A longitudinal population-based study. Eur J Clin Pharmacol 2002 58(4):285-291.

5 Stricker BC, Psaty BM. Detection, verification, and quantification of adverse drug reactions. Br Med J 2004 07;329(7456):44-47.

6 Wieringa NF, De Graeff PA, Van Der Werf GT, Vos R. Cardiovascular drugs: Discrepancies in demographics between pre- and post-registration use. Eur J Clin Pharmacol 1999 55(7):537-544.

7 Martin K, Bégaud B, Latry P, Miremont-Salamé G, Fourrier A, Moore N. Differences between clinical trials and postmarketing use. Br J Clin Pharmacol 2004 57(1):86-92.

8 World Health Organisation. The importance of pharmacovigilance. Safety monitoring of medicinal products. 2002; Available at: http://apps.who.int/medicinedocs/pdf/s4893e/s4893e.pdf. Accessed 3 January, 2013.

9 European Commission. Volume 9A of the rules governing medicinal products in the European Union. Guidelines on Pharmacovigilance for medicinal products for human use. 2008; Available at: http://ec.europa.eu/health/files/eudralex/vol-9/pdf/vol9a_09-2008_en.pdf. Accessed 3 January, 2013.

10 European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Module XV - Safety communication. 2012; Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500130396.pdf. Accessed 3 January, 2013.

11 Mol PGM, Straus SMJM, Piening S, De Vries JTN, De Graeff PA, Haaijer-Ruskamp FM. A decade of safety-related regulatory action in the Netherlands: A retrospective analysis of direct healthcare professional communications from 1999 to 2009. Drug Saf 2010 33(6):463-474.

12 Medicines Evaluation Board. Annual report 2011. 2012; Available at: http://www.cbg-meb.nl/NR/rdonlyres/35387CF6-5850-4A1A-B8FD-0909DAA34A93/0/CBGjaarverslag201120120522.pdf. Accessed 3 January, 2013.

13 Arnardottir AH, Haaijer-Ruskamp FM, Straus SMJ, Eichler H-, de Graeff PA, Mol PGM. Additional safety risk to exceptionally approved drugs in Europe? Br J Clin Pharmacol 2011 72(3):490-499.

14 Goldman SA. Communication of medical product risk: How effective is effective enough? Drug Saf 2004 2004 27(8):519-534.

15 Woosley RL. Drug labeling revisions - Guaranteed to fail? J Am Med Assoc 2000 12;284(23):3047-3049.

16 Yu DT, Seger DL, Lasser KE, Karson AS, Fiskio JM, Seger AC, et al. Impact of implementing alerts about medication black-box warnings in electronic health records. Pharmacoepidemiol Drug Saf 2011 20(2):192-202.
17 Weatherby LB, Walker AM, Fife D, Vervaet P, Klausner MA. Contraindicated medications dispensed with cisapride: Temporal trends in relation to the sending of 'Dear Doctor' letters. Pharmacoepidemiol Drug Saf 2001 10(3):211-218.
18 Guo JJ, Curkendall S, Jones JK, Fife D, Goehring E, She D. Impact of cisapride label changes on codispensing of contraindicated medications. Pharmacoepidemiol Drug Saf 2003 12(4):295-301.
19 Fischhoff B, Brewer NT, Downs JS. Communicating risks and benefits. An evidence-based user's guide. 2011; Available at: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM268069.pdf.
20 Child TJ, Mackenzie IZ, Rees M. Terminations of pregnancy, not unplanned deliveries, increased as result of pill scare [2]. Br Med J 1996 313(7063):1005.
21 Skjeldestad FE. Increased number of induced abortions in norway after media coverage of adverse vascular events from the use of third-generation oral contraceptives. Contraception 1997 55(1):11-14.
22 Wood R, Botting B, Dunnell K. Trends in conceptions before and after the 1995 pill scare. Popul Trends 1997 (89):5-12.
23 European Medicines Agency. European Medicines Agency finalises review of antidepressants in children and adolescents. 2005; Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/SSRI_31/WC500013082.pdf. Accessed 3 January, 2013.
24 U.S. Food and Drug Administration. Historical information on antidepressant use in children, adolescents, and adults. 2010; Available at: http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm096293.htm. Accessed 3 January, 2013.
25 Gibbons RD, Brown CH, Hur K, Marcus SM, Bhaumik DK, Erkens JA, et al. Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. Am J Psychiatry 2007 164(9):1356-1363.
26 Olfson M, Marcus SC, Druss BG. Effects of food and drug administration warnings on antidepressant use in a national sample. Arch Gen Psychiatry 2008 65(1):94-101.
27 Valuck RJ, Libby AM, Orton HD, Morrato EH, Allen R, Baldessarini RJ. Spillover effects on treatment of adult depression in primary care after FDA advisory on risk of pediatric suicidally with SSRIs. Am J Psychiatry 2007 164(8):1198-1205.
28 Bahri P, Harrison-Woolrych M. Focusing on risk communication about medicines: Why now? Drug Saf 2012 35(11):971-975.
29 The European Parliament and The European Council. DIRECTIVE 2010/84/EU. 2010; Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0074:0099:EN:PDF. Accessed 3 January, 2013.
30 The European Parliament and The European Council. REGULATION (EU) No 1235/2010. 2010; Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0001:0016:EN:PDF. Accessed 3 January, 2013.
31 Slovic P. Perceived risk, trust, and democracy. Risk Anal 1993 13(6):675-682.
32 Fischhoff B. Risk Perception and Communication Unplugged - 20 Years of Process. Risk Analysis 1995 15(2):137-145.

33 Breakwell GM. Risk communication: Factors affecting impact. Br Med Bull 2000 56(1):110-120.
34 Walaski P. Risk and Crisis Communications : Methods and Messages. Hoboken, NJ, USA: John Wiley & Sons, Inc.; 2011.
35 Lundgren, R.E. & McMakin, A.H. Risk Communication. A handbook for communicating environmental, safety, and health risks. Third edition. ed. Columbus, Ohio, USA.: Battelle Press; 2004.
36 Kasperson RE, Renn O, Slovic P, Brown HS, Emel J, Goble R, et al. The social amplification of risk: A conceptual framework. Risk Anal 1988 8(2):177-187.
37 Slovic P, Finucane ML, Peters E, MacGregor DG. Risk as Analysis and Risk as Feelings: Some Thoughts about Affect, Reason, Risk, and Rationality. Risk Anal 2004 24(2):311-322.
38 Slovic P, Peters E, Finucane ML, MacGregor DG. Affect, risk, and decision making. Health Psychol 2005 24(4 SUPPL.):S35; S40.
39 Ropeik D, Slovic P. Risk communication: a neglected tool in protecting public health. Risk in Perspective 2003 11(2).
40 Renn O. Three decades of risk research: accomplishments and new challenges. Journal of Risk Research 1998 1(1):49-71.
41 Slovic P. Perception of risk. Science 1987;236(4799):280-5.
42 McComas KA. Defining moments in risk communication research: 1996-2005. J Health Commun 2006 11(1):75-91.
43 Lofstedt RE. The impact of the Cox-2 inhibitor issue on perceptions of the pharmaceutical industry: Content analysis and communication implications. J Health Commun 2007 12(5):471-491.
44 Slovic P. The Perception of risk. 2011th ed. London: Earthscan; 2000.
45 Bahri P. Public pharmacovigilance communication: A process calling for evidence-based, objective-driven strategies. Drug Saf 2010 33(12):1065-1079.

Part 1

The impact of safety-related regulatory action

Chapter 2

Impact of safety-related regulatory action on clinical practice. A systematic review.

Sigrid Piening[1]
Flora M. Haaijer-Ruskamp[1]
Jonie T.N. de Vries[1]
Menno E. van der Elst[2]
Pieter A. de Graeff[1,2]
Sabine M.J.M. Straus[2,3]
Peter G.M. Mol[1,2]

Drug Safety 2012 35:5 (373-385)

[1] Department of Clinical Pharmacology, University Medical Center Groningen, Groningen, the Netherlands
[2] Dutch Medicines Evaluation Board, The Hague, the Netherlands
[3] Department of Medical Informatics, Erasmus University Medical Center, Rotterdam, the Netherlands

Abstract

Background: After market approval, new serious safety issues are regularly identified for drugs that lead to regulatory action to inform healthcare professionals. However, the effectiveness of these safety-related regulatory actions is under question. We currently lack a comprehensive overview of the effects of these drug safety warnings on clinical practice to resolve the debate about their effectiveness. The aim of this systematic review is to provide an overview of studies that assessed the impact of safety warnings.
Methods: A systematic search was performed for articles assessing the impact of Direct Healthcare Professional Communications or 'Dear Doctor' letters, Black Box Warnings and Public Health Advisories on clinical behaviour published between January 1996 and January 2010. The following variables were extracted: publication year, country, name of the drug, safety issue, specific safety warning (Direct Healthcare Professional Communication/Black Box Warning/Public Health Advisory), effect (intended/unintended) of the safety warning, outcome measure and study design. Papers were checked for several quality aspects. Study data were summarized using descriptive analyses.
Results: A total of 50 articles were identified. Two articles assessed two different drugs and were therefore counted twice (N=52). Thirty-three articles described the impact of safety warnings issued for three drugs and drug groups, i.e. third-generation oral contraceptives, cisapride and selective serotonin reuptake inhibitors. The remaining 19 articles described a broad variety of 14 drugs and drug groups. Twenty-five studies applied an interrupted time series design, 23 a controlled or uncontrolled before/after design, and four articles applied both. None of the articles could rule out the influence of confounding factors. The intended effects were reported in 18 (72%) of the 25 before/after analyses, whereas only 11 (41%) of the 27 interrupted time series analyses reported an impact. Only two (8%) of the before/after analyses against 11 (41%) of the interrupted time series analyses reported mixed impacts. When unintended effects were assessed in case of selective serotonin reuptake inhibitors and third-generation oral contraceptives, these were almost always present: in 19 of 22 and 4 of 5 articles, respectively. Our review shows that safety-related regulatory action can have some impact on clinical practice but firm conclusions are difficult to draw. Evidence is primarily based on three drugs and drug groups. Almost half of the studies had inadequate before/after designs and the heterogeneity in analyses and outcome measures hampered the reporting of overall effect sizes. Studies with adequate interrupted time series design reported a more mixed impact of safety warnings than before/after studies. Furthermore, this review shows the relevance of considering not only the intended but also the unintended effects of safety warnings.

Conclusions: There is a clear need for further research with appropriate study designs and statistical analyses, with more attention to confounding factors such as media coverage, to understand the impact of safety-related regulatory action.

Introduction

Knowledge of the full benefit-risk profile of a drug at the time of market approval is incomplete. Pre-registration trials are limited in establishing the full safety profile of new drugs due to, for example, small sample size, short duration, and a homogeneous study population.[1,2] In approximately 10% of all marketed drugs, safety-related regulatory action is required for new and serious safety issues[3-5] leading to hospitalization, disability or even death.[6,7] With these safety warnings, healthcare professionals and patients are informed of these safety issues or even of the possible withdrawal of the drug from the market.

Regulatory authorities and the pharmaceutical industry employ several safety warnings to inform healthcare professionals of serious safety issues of drugs.[8] The summary of product characteristics can be updated with new safety information. Public Health Advisories (US only) permit the notification of patients and physicians of a serious safety issue to improve selection of medication. A Black Box Warning (US only) highlights a drug's potential safety issues in a framed box on the label and the patient package inserts. A Direct Healthcare Professional Communication (DHPC; in the EU) and Dear Healthcare Professional letter (in the US) or 'Dear Doctor' letter (further referred to as a DHPC) is a paper-based personalized mailing to healthcare professionals. Finally, a drug can be withdrawn from the market due to a safety issue when the benefits of a drug no longer outweigh its risks.

The effectiveness of safety warnings has been criticized.[9,10] Previous research concluded that safety warnings can be effective, albeit not always and not always sufficiently.[10] Additionally, safety warnings have resulted not only in intended, but also in unintended effects. The safety warnings for selective serotonin reuptake inhibitors resulted in intended reduced prescription in the population at risk after the identification of an increased risk of suicidality and suicidal thoughts in children and adolescents.[11] Unfortunately, some unintended effects were also reported. The prescription of selective serotonin reuptake inhibitors decreased in adults as well,[12-14] possibly associated with a temporal increase in suicidality in the general population,[12] although these results have been contradicted.[15]

The experience with selective serotonin reuptake inhibitors indicates that several inventories of effectiveness of safety warnings have been performed, but with various results. The overall effect of safety warnings is unclear. Since the monitoring of the outcome of risk minimization measures will become mandatory in the near future, such an overview is required.[16,17] To that end, we performed a systematic review of the effects

– both intended and unintended – of safety warnings on clinical practice. In this review, we specifically targeted DHPCs, Black Box Warnings and Public Health Advisories when referring to safety warnings.

Methods

Search strategy

A systematic search for articles published between January 1996 and January 2010 evaluating the impact of DHPCs, Black Box Warnings and Public Health Advisories safety-related regulatory actions was performed in three steps. First, index terms and free text words were identified from an initial set of papers retrieved by random search. Based on the terms used in these articles, we systematically searched the online literature databases MEDLINE and EMBASE for relevant papers without any language restrictions (**Table 1**).

Table 1. Search strategy

		And	And	And
Step 1 Systematic literature search	((drug information* OR drug information) OR (drug labelling* OR drug labelling) OR (drug surveillance program* OR drug surveillance program) OR (drug monitoring* OR drug monitoring) OR (drug contraindication* OR drug contraindication))	(letter* OR communicat* OR dear doctor OR warning*)	((clinical study* OR clinical study) OR (time series analysis* OR time series analysis) OR (controlled study* OR controlled study))	year [1996-2009]
Step 2: DHPC search	(active substance OR brand name)	safety issue	(clinical study* OR time series analysis* OR controlled study*)	[year DHPC publication]
Step 3: Snowballing and first author check	references included papers were hand searched	-	-	-
	'1st Authors' last name initial(s).'/au	-	-	year [1996-2009]

Underlined terms were adjusted according to specific drug/safety issue for which the DHPC was issued, or the author.
DHPC = Direct Healthcare Professional Communication.

A second search in MEDLINE and EMBASE was performed based on drugs with a DHPC in the Netherlands. We added this step because the initial analyses indicated that we were missing relevant publications. As a third step, the included papers' references were checked (snowballing) and a first author search was performed to search for additional relevant papers.

Two reviewers (SP/JV and PM) independently evaluated all the papers identified for eligibility. A first selection was based on titles and abstracts and a second and final selection was based on examination of each full paper. Any disagreements were resolved during consensus meetings with a third reviewer (SS/ME).

Inclusion and exclusion criteria

Only randomized trials, quasi experiments (interrupted time series and controlled or uncontrolled before/after studies) evaluating the impact of DHPCs, Black Box Warnings and/or Public Health Advisories on clinical practice were included. In randomized trials the impact of an intervention is assessed by comparing an intervention group to a randomly assigned control group. Both groups are exposed to the same biases and therefore considered alike, permitting the assessment of the causal effect of an intervention. Before/after studies are used to measure the impact of safety warnings at three or fewer time points both before and after the intervention. Interrupted time series designs have data collected at multiple instances (preferably >20 data points) before and after an intervention, with the advantage that they can detect whether an intervention has an effect significantly greater than underlying secular trends.[18]

Cross-sectional articles evaluating only the situation after a safety warning were excluded since no comparative impact could be estimated. For example, articles only evaluating a safety warning in cases of a withdrawal of a drug were excluded, since clinical behaviour will change by definition and the article would therefore cause bias. Opinion articles, surveys, reviews, duplicates in different languages and publications of non-original data were excluded to avoid publication bias.[19]

Data extraction

Five reviewers (SP, JV, ME, FT and PM working in varying pairs) systematically extracted the following variables: publication year, country, drug name, safety issue, effect (intended/unintended), study design, safety warning type (DHPC/Black Box Warning/Public Health Advisory) and outcome measure. The Cochrane Effective Practice and Organisation of Care Review Group (EPOC) quality criteria for interrupted time series studies score list was used to check the quality aspects of the studies.[20] The same quality aspects were scored for before/after papers, except for items that were only applicable to interrupted time series design studies. Again, any disagreements were resolved by consensus or, if necessary, by a third reviewer.

The main goal of a safety warning, i.e. to minimize occurrence of the issue, was defined as its intended effect – for instance, to prevent prescription to specific patient groups (e.g. selective serotonin reuptake inhibitors to adolescents/children), to prevent

co-prescription in case of a drug-drug interaction (e.g. cisapride and macrolides increasing the risk of QT prolongation), or to promote baseline/follow-up laboratory tests (e.g. liver function testing with troglitazone use).

Unintended effects were defined as unforeseen or unintended, for instance, an increase in suicides after the issuance of warnings restricting the use of selective serotonin reuptake inhibitors in children and adolescents.

The effect of a safety warning was scored on the authors' reports, i.e. a safety warning had an effect, no effect or mixed effects. Mixed effects were defined as an effect for one outcome measure but no effect for another.

Data analysis

Data were summarized according to the following variables: drug group, assessed impact, study design, safety warnings type and outcome measure, using descriptive analyses. The quality of the included studies was scored by adding up each quality aspect that was met. The studies were counted in different ways for each variable:

- Drug group: if an article assessed a safety warning for more than one drug, the article was assigned to all relevant drugs and drug groups. In that case the study was counted more than once.
- Assessed impact: the impact of a safety warning was split into intended and unintended impacts.
- Study design: if one study assessed several outcome measures with different study designs, the result of each individual outcome measure was attributed to the related study design. In such cases a study design was counted more than once.
- Type of safety warning: in papers assessing more than one safety warning, the effect of each safety warning was assessed separately. If more than one safety warning was evaluated, but only one overall effect was presented, the overall effect was attributed to each individual safety warning.
- Outcome measure: if one study assessed several outcome measures, the impact of a safety warning was counted for each individual outcome measure. Consequently, when an impact was observed on drug use but not on a more specific outcome measure such as conducted laboratory tests, the effect of that safety warning was categorized as a mixed effect.

Results

A total of 4086 papers were identified using the first search strategy, of which 215 papers were selected for full-text examination resulting in the inclusion of 34 papers for detailed analysis (**Figure 1**).

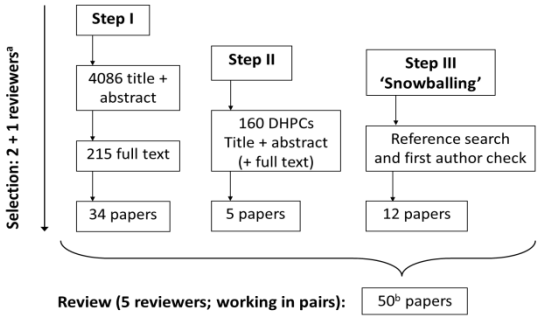

Figure 1. Search results
a Two reviewers independently evaluated the papers, with a third reviewer adjudicating in a consensus meeting when there was disagreement regarding the eligibility of a study. **b** Two of 50 papers evaluated safety-related regulatory action for two different drugs and drug groups (Wilkinson et al.,[21] Starner et al.[22]).
DHPC = Direct Healthcare Professional Communication

The second step, based on the safety issues mentioned in 160 DHPCs issued in the Netherlands, yielded a further five eligible papers. Snowballing yielded another eleven papers. In total 50 papers were included. In two papers[21,22] two different drugs and drug groups were assessed, therefore each paper was counted twice in further analyses (n=52).The main results of the data extraction are shown in **Table 2** and the key variables of the individual studies are shown in the **Appendix table**.

Drug Group

Three different drugs and drug groups, i.e. third-generation oral contraceptives (increased risk of thrombosis, published 1996-1999;[23-31] cisapride (risk of serious cardiac arrhythmias, published 2000-2005);[21,32-39] and selective serotonin reuptake inhibitors (risk of suicide in adolescents and children, published 2005-2009)[11-15,40-49] accounted for 33 articles in our review (**Table 2**). The remaining 19 papers described a broad variety of 14 different drugs and drug groups.[7,21,22,50-64]

Table 2. Study characteristics

Key study characteristics	Number of studies (N=52) [N; %]	References
Country		
USA	26 (50)	7,13,14,21,22,32-35,40-44,49,50-58
EU	19 (37)	11,15,23-31,36-38,45,59-62
Other	7 (13)	12,39,46-48,63,64
Drug or drug group		
SSRI	15 (29)	11-15,40-49
Third gen. O.C.	9 (17)	23-31
Cisapride	9 (17)	21,32-38,56
Terfenadine	3 (6)	50-52
Troglitazone	3 (6)	7,21,53
Tramadol	2 (4)	54,58
Other	11 (21)	22,54,56,57,59-64
Assessed impact		
Intended effect	40 (77)	7,11,21,22,32-35,40,41,43,44,50-58
Unintended effect	4 (8)	23,27,30,42
Both intended & unintended effect	8 (15)	12-15,29,45,46,49
Study design		
ITS	25 (48)	13,14,21,30,32,34,35,39-43,45,47,48,52,54,56,57,59,61,63,64
BA	23 (44)	7,11,12,15,23-27,29,31,33,36-38,44,46,50,53,55,58
ITS & BA	4 (8)	22,28,49
Safety warning (N=97)[a]		
DHPC	65 (67)	7,11,12,15,21,23-40,42,45,47,48,50-57,58-64
BBW	15 (15)	12,14,22,40-42,44,47,50,51,55-57
PHA	17 (18)	12-14,41-43,46,47,49,59
Outcome measure (N=77)[a]		
Drug use (volume)	35 (45)	11-14,21,22,24-26,28-31,36,39,41,45-49,56,57,59,63,64
CI use/DDI	17 (22)	22,32-38,50-52,54,57,58
Laboratory testing	4 (5)	7,53,55,56
Spont. ADE reporting	2 (3)	60,61
Care	7 (9)	13,15,41,43,46,49,59
Other	12 (16)	12,15,23,25,27-29,42,44-46,59

a The numbers of evaluated safety warnings and outcome measures are larger than the number of included studies as several studies evaluated more than one safety warnings and/or outcome measure.
USA = United States of America; **EU** = European Union; **SSRI** = Selective serotonin reuptake inhibitors; **Third gen. O.C.** = Third generation oral contraceptives; **ITS** = Interrupted Time Series; **BA** = Before/After study or ITS with less than 3 data points before or after an intervention; **DHPC** = Direct Healthcare Professional Communication; **BBW** = Black Box Warning; **PHA** = Public Health Advisory; **CI/DDI** = Contraindicated use/Drug-Drug Interaction; **ADE** = Adverse Drug event.

Assessed Impact

An intended effect was observed in 9 of 14 articles[(11-15,40,41,43-49)] in which the intended effect of safety warnings for selective serotonin reuptake inhibitors was assessed (**Figure 2**). These intended effects primarily concerned (large) decreases of the volume of drug use in children and adolescents, but also improved psychiatric care (**Appendix table**). Intended

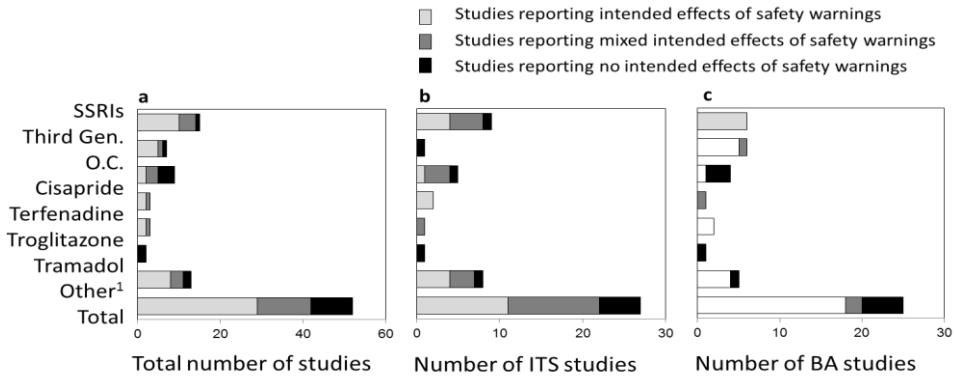

Figure 2. Study design and intended effects per drug and drug group.
1 'Other' includes: antipsychotics, infliximab, isotretinoin, nimesulide, pemoline, pioglitazone, rosiglitazone, statins, telithromycin, ticlopidine. Panel (a) reports the effects of all included studies (N=52); panel (b) of ITS studies only (N=27); and (c) BA studies alone (N=25). Two papers evaluated safety-related regulatory action for two drugs and drug groups (Wilkinson et al.,[21] Starner et al.[22]) and four papers used both ITS and BA analyses for different outcome measures (Libby et al.,[49] Farmer et al.,[28] Starner et al.[x2][22]) and are therefore represented twice. Four articles assessed only unintended effects of safety warnings and are therefore not reflected in this figure (Forrester et al.,[42] Child et al.,[23] Williams et al.,[30] Wood et al.[27]).
BA= before/after study or ITS with less than three data points before or after an intervention; **ITS**=Interrupted Time Series; **SSRIs**= selective serotonin reuptake inhibitors; **Third-gen. O.C.**= third-generation oral contraceptives.

effects of a safety warning issued for third-generation oral contraceptives were assessed in six articles.[24-26,28,29,31] In four of these six articles[24,26,29,31] strong reductions in the use of third-generation oral contraceptives were reported and/or a shift in use towards second-generation oral contraceptives. The remaining two articles[25,28] reported mixed impact; a reduction in drug use was observed but no changes in venous thromboembolism cases and discontinuation rates/switches were reported. In the case of cisapride, 7 of 17 assessed DHPCs[21,32,35,38,39] presented intended effects, and 9[32-37] showed no intended effects (reduced drug use volume or contraindicated drug use). One DHPC showed mixed results. While no effect was observed for overall use of the DHPC, an effect was observed for new users of cisapride.[21] The early US DHPCs (1995 and 1996) and the Italian 1998 DHPC lacked impact, whereas subsequent US DHPCs (1998 onwards) and the Dutch and New Zealand DHPCs did achieve their intended effects (**Appendix table**).

Articles published on safety warnings issued for the remaining drugs and drug groups reported effects as intended to a varying degree. The three papers assessing terfenadine safety warnings[50-52] reported intended effects on contraindicated drug use, except for contraindicated concomitant use of ketaconazole, which did not decrease.[50] Two of three troglitazone papers reported intended increases in laboratory testing after the safety warnings.[53,65] In the remaining publications a decrease in filled prescriptions was

observed only for new drug users and not for all drug users, explained by a higher sensitivity to detect changes in prescriptions for new users.[21] The warning for tramadol failed to achieve the intended decrease in contraindicated drug use.[54,58]

Unintended effects were evaluated for safety warnings issued for selective serotonin reuptake inhibitors and third-generation oral contraceptives. In the 12 publications addressing possible unintended effects, of which four only assessed unintended and no intended effects,[23,27,30,42] nearly all warnings for selective serotonin reuptake inhibitors (19 of 22 warnings)[12-14,42,45,46] and all four warnings for third-generation oral contraceptives[23,27,29,30] showed unintended effects.

Study Design

No randomized controlled trials, or controlled before/after studies were identified that assessed the intended or unintended impact of safety warnings. Of those studies evaluating the intended effects, 23 papers applied an interrupted time series design and 21 a before/after design (**Table 2**). Four papers applied both interrupted time series and before/after designs for different outcome measures.[22,28,49] These articles are counted twice with respect to our study design analysis, leading to a total of 25 before/after and 27 interrupted time series analyses.

Overall, intended effects were reported in 29 (56%) of 52 analyses (**Figure 2**). While only 11 (41%) of 27 interrupted time series analyses reported an impact, such intended effects were reported in 18 (72%) of 25 before/after analyses. Eleven (41%) interrupted time series and two (8%) before/after analyses reported mixed impact.
All six papers assessing the intended effects of safety warnings on third-generation oral contraceptives had a before/after design (**Figure 2**), one paper also included an interrupted time series analysis where no impact of the warning on venous thromboembolism cases was reported (**Appendix table**).[28] Seventeen interrupted time series and 13 before/after designs were used in the remaining studies. The nine interrupted time series analyses for safety warnings on selective serotonin reuptake inhibitors, mainly reported effects (four articles)[13,45,48,49] and mixed effects (four articles).[14,40,41,47] The five interrupted time series analyses assessing cisapride warnings primarily reported mixed effects (three articles)[21,32,35] for the different warnings that were evaluated.

Unintended effects of the evaluated safety warnings were reported in five of six analyses for both interrupted time series and before/after analyses.

Regarding the quality assessment of the papers, interrupted time series papers scored on average 6.7 out of 8 quality aspects, ranging from 3 to 7 of 8 (**Appendix table**). Before/after papers had a similar average score of 4.6 of 6 quality aspects, ranging from 3

to 5 of 6. All papers used a reliable outcome measure. However, none of the papers could rule out the influence of confounding factors such as media attention. Of the 29 analyses applying the stronger interrupted time series design, 21 used appropriate statistics.

The Type of Safety Warning

Ninety-seven safety warnings were assessed in the 52 articles, ranging from 1 to 8 warnings per paper and 1 to 13 warnings per drug or drug group (**Appendix table**). Twenty-one papers evaluated more than one safety warning.[12,14,15,21,22,32,34,35,40-42,47,50,51,53,55,56,59,62,63,65] The DHPC was the most frequently evaluated warning (65 of 97 warnings), with similar numbers of Black Box Warnings (15) and Public Health Advisories (16) evaluated (**Table 2**).

Intended effects were evaluated in 91 cases: 52 (57%) showed an impact, 24 (26%) did not and 15 (16%) had mixed effects (**Figure 3**).

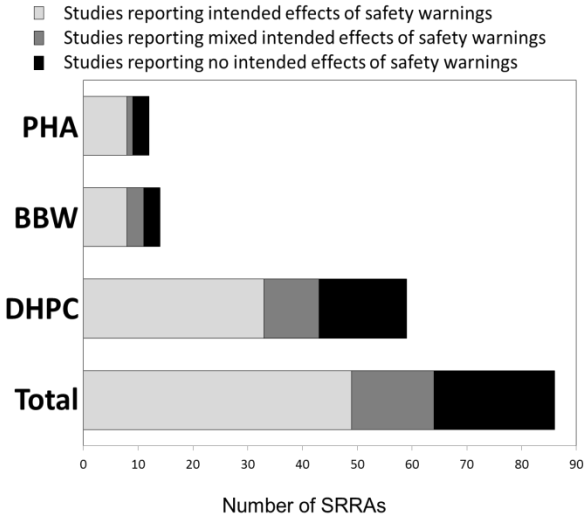

Figure 3. Safety warnings and intended effects (N=86).
Two papers evaluated warnings for two drugs and drug groups (Wilkinson et al.,[21] Starner et al.[22]) and four papers used both ITS and BA analyses for different outcome measures (Libby et al.,[49] Farmer et al.,[28] Starner et al.[x2][22]), and are therefore represented twice. The number of evaluated warnings is larger than the number of included studies, as several studies evaluated more than one safety warning (see Appendix table).
BA= before/after study or ITS with less than three data points before or after an intervention; **BBW**= Black Box Warning; **DHPC**= Direct Healthcare Professional Communication; **ITS**=Interrupted Time Series; **PHA**= Public Health Advisory; **SRRAs=** Safety-Related Regulatory Action.

In our study, DHPCs, Black Box Warnings and Public Health Advisories had similar patterns of impact as intended by the warnings, showing an effect in 56%, 57% and 61%, respectively, with no effect in 27%, 21% and 31%, respectively, or a mixed effect in 17%, 21% and 8%, respectively.

Effects were reported for nearly all (86%) safety warnings evaluating unintended effects but assessment was limited to selective serotonin reuptake inhibitors and third-generation oral contraceptives (**Appendix table**). Only DHPCs were issued for third-generation oral contraceptives, while selective serotonin reuptake inhibitors received DHPCs, Black Box Warnings and Public Health Advisories. No variation in impact was observed across the different safety warnings.

Outcome Measures

The 52 articles in our study assessed the impact of safety warnings for 77 outcome measures. The majority (28) of articles assessed the intended impact of warnings on clinical behaviour by evaluating overall drug use volume (**Appendix table**).[11,12,14,15,21,22,24-26,28,29,31,36,39-41,45-47,49,56,57,59] In some articles more specific drug use measures were assessed: drug-drug interaction/contraindicated use (16 articles),[22,32-38,50-52,54,57,58,62] drug use in defined populations (adults, children, etc.) (16 articles),[11,12,14,15,25,28,29,31,40,41,44-49] new users of a drug (1 article),[21] refusal of antidepressant prescription (1 article),[44] or discontinuation rates/switches (1 article).[25] Nine studies assessed care-related outcomes such as the type of healthcare professional (e.g. general practitioner, psychiatrist), diagnosing patterns (5 articles),[13,41,43,49,59] and adherence to performing warning-dictated laboratory tests (4 articles).[53,55,56,65] These papers specifically intended to evaluate the non-drug treatment recommendations of a warning. Additionally, in five papers clinical outcome measures were assessed, e.g. venous thromboembolism cases (1 article),[28] mortality (1 article),[59] hospital admissions (1 article)[59] and spontaneous adverse drug event reports (2 articles).[60,61]

In eight studies the use of multiple outcome measures led to mixed intended effects (**Appendix table**).[21,25,28,41,50,56,57,59] For six of these eight articles, impact was observed on the volume of drug use in general but not for more specific outcome measures such as drug use outcomes, e.g. only new users of troglitazone,[21,25,57] healthcare outcomes such as laboratory tests because of hepatoxicity risks,[56,59] and clinical outcomes such as venous thromboembolism cases in third generation oral contraceptives.[28,59] The remaining two articles only reported the impact of safety warnings on one of two contraindicated concomitantly used drugs,[50] and the impact of two of the three assessed warnings on the volume of drug use.[59]

The outcome measures for the unintended effects of safety warnings were matched with the specific message of a warning (**Appendix table**). All three publications assessing spillover effects (decreased drug use by the non-targeted adult population) of the selective serotonin reuptake inhibitor warnings reported effects.[12-14]

The outcome measures related to suicide and suicidal thoughts (self-poisoning, suicide rates and hospital admissions) showed more varied results. Two articles reported increases in self-poisoning cases;[42,45] but of three articles assessing suicide rates,[12,15,46] one[15] reported no increase. The latter study also found no increase in hospital admissions for self-harm.[15] Lastly, impact was found on health services use, as shown by a decrease in the rate of physician visits after the safety warning.[46]

Both articles assessing abortions after a safety warning for third-generation oral contraceptives reported increases in the number of abortions.[23,29] In addition, an increase in conceptions was observed.[27] Moreover, a decrease in third-generation oral contraceptive use was observed in Ireland, although this was not in line with recommendations by national authorities.[30]

Discussion

This systematic review provides the first overview of articles published on the effect of safety warnings. We identified 52 studies that assessed the impact of safety warnings on clinical practice. Intended effects were found in the majority of cases but varied between drugs and drug groups. Unintended effects were also reported. No firm conclusions on effect size can be drawn due to a number of factors, including the small number of drug groups evaluated, deficiencies in the study design and inconsistency in outcome measures.

The available studies mainly assessed three drug groups: selective serotonin reuptake inhibitors, third-generation oral contraceptives and cisapride. The focus on these drug groups is in line with the extensive media attention that two of these safety related issues received. The studies included indicated that the so-called ‘pill scare’ had a very large impact, specifically in the UK[23-28] after the UK Committee of Safety of Medicine advised discontinuation of third-generation oral contraceptive use. Consequently, the warnings resulted in a similar impact in adjacent countries that had taken a less rigorous approach.[30] A BBC broadcast[66] in the UK about self-harm and suicide related to the selective serotonin reuptake inhibitor paroxetine caused further media attention in several countries, which was followed by an extensive reassessment of the benefits and risks associated with the product group and a number of successive regulatory actions, especially in the US.[67] The debate about cisapride seems to have been triggered by the

potential preventability of prescribing concomitant contraindicated drugs, but did not generate as much public interest.

Data related to selective serotonin reuptake inhibitors and third-generation oral contraceptives also shows that the observed impact was not always as intended, which highlights the relevance of taking not only the intended but also the unintended effects into account. Of eight selective serotonin reuptake inhibitor papers evaluating the unintended effects of the warnings, six identified unintended effects such as increases in suicide rates and unintended spillover effects, in particular decreased use of antidepressants in adults. Unintended effects of the warnings were also found for third-generation oral contraceptives: increases in conceptions and abortion rates were observed. The concerns surrounding this specific safety issue caused many women to switch to other oral contraceptives or to cease using oral contraceptives all together.

How to present risk to the general public was extensively discussed as a result of the 'pill scare'. The risk of venous thromboembolism with third generation oral contraceptive use was presented as doubling. This implied a large increase in risk, although the absolute risk of venous thromboembolism was still smaller than that of venous thromboembolism during pregnancy. Afterwards, restrictions on third-generation oral contraceptive use were withdrawn in the UK and the wording of the warning was adjusted.[68]

Almost half of the studies applied a before/after design, which coupled with heterogeneity in the analyses and outcome measures hampered reporting of overall effect sizes of safety warnings. Inclusion of before/after studies could be considered a limitation due to their inherent methodological flaws.[69] For example, with a before/after study design it is not possible to control for seasonal changes in drug use. However, it is suggested that using a before/after design could be valid where a comparable control group is used to assess any differences between the groups that could be attributed to the intervention.[70] Notwithstanding that, all papers with before/after design were included in the systematic review to provide a comprehensive overview of what had been evaluated to date. Interrupted time series design is the best available study design to evaluate the impact of policy changes where it is almost impossible to employ a control group, and it is regarded as the 'strongest' quasi-experimental study design.[71] When considering the interrupted time series studies alone, the most apparent intended effects of safety warnings were observed in the case of terfenadine through a decrease in contraindicated drug use. In cases of the selective serotonin reuptake inhibitors and cisapride, the majority of interrupted time series studies reported mixed effects, mainly regarding the volume of drug use.

The interpretation of results is further complicated because of the assessment of different outcome measures (e.g. drug use/contraindicated drug use/laboratory

tests/spontaneous adverse drug event reports), different interventions (DHPCs/Black Box Warnings/Public Health Advisories), and the heterogeneity of analyses. However, since the warnings can have different intentions, assessing specific outcome measures regarding the safety issue in question is a more accurate method to detect the intended impact of a warning. For example, where a DHPC is issued to address an increased hepatoxicity risk, with a recommendation for testing the liver function of patients, assessing the impact on laboratory tests could be more appropriate than simply assessing drug use.

In addition, the majority of the papers included did not assess every safety warning that was issued for the drugs and drug groups. Sometimes, warnings were preceded by or coincided with other warnings regarding the same safety issue, and which were not analysed in the study. This was the case in the study by Gibbons et al.[12] in which several warnings issued between October 2003 and December 2006 were evaluated, although three other warnings issued within that period (between September and December 2005), were not assessed. These other warnings may have strengthened the safety message, the impact of which was assessed, and therefore have biased the results. Similarly, several articles reported an overall effect only, and lacked assessment of the effect by individual warnings. Therefore, our data do not allow the drawing of conclusions about which safety warning strategy is more effective, especially since two-thirds of the warnings evaluated concerned DHPCs.

A limitation of the outcome in all studies was that none of the papers could rule out the influence of confounding factors such as media attention, which could have strengthened the effect of the safety warnings. For example, in the case of the increased risk of suicide and suicidal thoughts in selective serotonin reuptake inhibitor use, the media hype that occurred could have been an influential factor on the effect of the safety warnings on drug use.[14,40,45]

The strength of this research was that it was extensive and comprehensive. Various search methods were used to minimize selection bias; searches were performed without any language restrictions and only the first or most relevant paper published on the same dataset was included.[19] Furthermore, we evaluated different safety warnings; papers assessing the effects of Black Box Warnings and Public Health Advisories, which were also commonly used to communicate safety problems of drugs in the US, were included as well as DHPCs.

Conclusions

Our review highlights the gap in the current knowledge on effectiveness of safety warnings and also shows the relevance of taking not only the intended effects but also the

unintended affects into account. There is a clear need for more research to understand the impact of safety warnings, using appropriate study designs and statistical analyses. Both the intended and the anticipated unintended effects of safety warnings should be assessed. Not only should the impact on drug use be evaluated, but also the impact on outcome measures that specifically evaluate the intention of the warning. Moreover, all individual warnings issued for the drug in question should be assessed instead of only a selection. The impact should be reported per warning instead of an overall effect. The interrupted time series study is the preferred study design as it allows for greater reliability in assessing the impact of safety warnings in comparison to before/after designs. When conducting a study with one drug or a limited selection of drugs, confounding factors should be better described and included in the analysis, which is possible with advanced interrupted time series analysis methods.

Acknowledgements

This study was supported by an unconditional grant from the Dutch Medicines Evaluation Board (College ter Beoordeling van Geneesmiddelen [CBG]-MEB). The authors, who are also (part-time) employees of the MEB (ME, PG, SS and PM), state that the opinions presented in this paper are their own and do not necessarily reflect that of the MEB. All authors report that they do not have any conflicts of interest. The authors thank F. Sayed Tabatabaei (FS) for his contribution to the data extraction.

References

1 Califf RM. Benefit assessment of therapeutic products: The Centers for Education and Research on Therapeutics. Pharmacoepidemiol Drug Saf 2007 16(1):5-16.

2 Stricker BC, Psaty BM. Detection, verification, and quantification of adverse drug reactions. Br Med J 2004 07;329(7456):44-47.

3 Mol PGM, Straus SMJM, Piening S, De Vries JTN, De Graeff PA, Haaijer-Ruskamp FM. A decade of safety-related regulatory action in the Netherlands: A retrospective analysis of direct healthcare professional communications from 1999 to 2009. Drug Saf 2010 33(6):463-474.

4 Lasser KE, Allen PD, Woolhandler SJ, Himmelstein DU, Wolfe SM, Bor DH. Timing of new black box warnings and withdrawals for prescription medications. J Am Med Assoc 2002 05;287(17):2215-2220.

5 Heemstra HE, Giezen TJ, Mantel-Teeuwisse AK, De Vrueh RLA, Leufkens HGM. Safety-related regulatory actions for orphan drugs in the US and EU: A cohort study. Drug Saf 2010 33(2):127-137.

6 Hawkey CJ, Langman MJS. Non-steroidal anti-inflammatory drugs: Overall risks and management. Complementary roles for COX-2 inhibitors and proton pump inhibitors. Gut 2003 04;52(4):600-608.

7 Graham DJ, Ouellet-Hellstrom R, Macurdy TE, Ali F, Sholley C, Worrall C, et al. Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. J Am Med Assoc 2010 07;304(4):411-418.

8 Giezen TJ, Mantel-Teeuwisse AK, Straus SMJM, Schellekens H, Leufkens HGM, Egberts ACG. Safety-related regulatory actions for biologicals approved in the United States and the European Union. J Am Med Assoc 2008 10;300(16):1887-1896.

9 Woosley RL. Drug labelling revisions - Guaranteed to fail? J Am Med Assoc 2000 12;284(23):3047-3049.

10 Goldman SA. Communication of medical product risk: How effective is effective enough? Drug Saf 2004 27(8):519-534.

11 Murray ML, Thompson M, Santosh PJ, Wong ICK. Effects of the committee on safety of medicines advice on antidepressant prescribing to children and adolescents in the UK. Drug Saf 2005 28(12):1151-1157.

12 Gibbons RD, Brown CH, Hur K, Marcus SM, Bhaumik DK, Erkens JA, et al. Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. Am J Psychiatry 2007 164(9):1356-1363.

13 Valuck RJ, Libby AM, Orton HD, Morrato EH, Allen R, Baldessarini RJ. Spillover effects on treatment of adult depression in primary care after FDA advisory on risk of pediatric suicidality with SSRIs. Am J Psychiatry 2007 164(8):1198-1205.

14 Olfson M, Marcus SC, Druss BG. Effects of food and drug administration warnings on antidepressant use in a national sample. Arch Gen Psychiatry 2008 65(1):94-101.

15 Wheeler BW, Gunnell D, Metcalfe C, Stephens P, Martin RM. The population impact on incidence of suicide and non-fatal self-harm of regulatory action against the use of selective serotonin reuptake inhibitors in under 18s in the United Kingdom: Ecological study. BMJ 2008 03;336(7643):542-545.

16 The European Parliament and The European Council. REGULATION (EU) No 1235/2010. 2010; Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0001:0016:EN:PDF. Accessed January 4, 2010.

17 The European Parliament and The European Council. DIRECTIVE 2010/84/EU. 2010; Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0074:0099:EN:PDF. Accessed January 4, 2011.
18 Ramsay CR, Matowe L, Grilli R, Grimshaw JM, Thomas RE. Interrupted time series designs in health technology assessment: Lessons from two systematic reviews of behavior change strategies. Int J Technol Assess Health Care 2003 19(4):613-623.
19 Khan KS, Ter Riet G, Glanville J, Sowden AJ, Kleijnen J. Undertaking Systematic Reviews of Research on Effectiveness. CRD's Guidance for those Carrying Out or Commissioning Reviews. March 2001; Available at: www.medepi.net/meta/guidelines/Overview_CRD_Guidelines.pdf. Accessed 8/25, 2009.
20 Cochrane Effective Practice and Organisation of Care Review Group. The data collection checklist. 2002; Available at: http://epoc.cochrane.org/sites/epoc.cochrane.org/files/uploads/datacollectionchecklist.pdf. Accessed April 13, 2011.
21 Wilkinson JJ, Force RW, Cady PS. Impact of safety warnings on drug utilization: Marketplace life span of cisapride and troglitazone. Pharmacotherapy 2004 24(8):978-986.
22 Starner CI, Schafer JA, Heaton AH, Gleason PP. Rosiglitazone and pioglitazone utilization from January 2007 through May 2008 associated with five risk-warning events. J Managed Care Pharm 2008 14(6):523-531.
23 Child TJ, Mackenzie IZ, Rees M. Terminations of pregnancy, not unplanned deliveries, increased as result of pill scare. Br Med J 1996 313(7063):1005.
24 Ferguson JJ, Jenkins MGV, Murty J, Firth S, Iversen O-, Nilsen ST. Effect of CSM's warning about safety of third generation oral contraceptives. Br Med J 1996 313(7053):363-364.
25 Martin RM, Hilton SR, Kerry SM. The impact of the October 1995 'pill scare' on oral contraceptive use in the United Kingdom: Analysis of a general practice automated database. Fam Pract 1997 14(4):279-284.
26 Roberts SJ. The immediate effects of the pill safety scare on usage of combined oral contraceptives in north east England. J Epidemiol Community Health 1997 51(3):332-333.
27 Wood R, Botting B, Dunnell K. Trends in conceptions before and after the 1995 pill scare. Popul Trends 1997 (89):5-12.
28 Farmer RDT, Williams TJ, Simpson EL, Nightingale AL. Effect of 1995 pill scare on rates of venous thromboembolism among women taking combined oral contraceptives: Analysis of General Practice Research Database. Br Med J 2000 08;321(7259):477-479.
29 Skjeldestad FE. Increased number of induced abortions in norway after media coverage of adverse vascular events from the use of third-generation oral contraceptives. Contraception 1997 55(1):11-14.
30 Williams D, Kelly A, Carvalho M, Feely J. Effect of the British warning on contraceptive use in the General Medical Service in Ireland. Ir Med J 1998 91(6):202-203.
31 De Vries CS, Van Den Berg PB, De Jong-Van Den Berg LTW. Oral contraceptive use before and after the latest pill scare in the Netherlands: Changes in oral contraceptive use and how users change. Contraception 1998 57(4):247-249.
32 Guo JJ, Curkendall S, Jones JK, Fife D, Goehring E, She D. Impact of cisapride label changes on codispensing of contraindicated medications. Pharmacoepidemiol Drug Saf 2003 12(4):295-301.
33 Smalley W, Shatin D, Wysowski DK, Gurwitz J, Andrade SE, Goodman M, et al. Contraindicated use cisapride: Impact of Food and Drug Administration regulatory action. J Am Med Assoc 2000 12;284(23):3036-3039.

34 Jones JK, Fife D, Curkendall S, Goehring Jr. E, Guo JJ, Shannon M. Coprescribing and codispensing of cisapride and contraindicated drugs. J Am Med Assoc 2001 10;286(13):1607-1609.

35 Weatherby LB, Walker AM, Fife D, Vervaet P, Klausner MA. Contraindicated medications dispensed with cisapride: Temporal trends in relation to the sending of 'Dear Doctor' letters. Pharmacoepidemiol Drug Saf 2001 10(3):211-218.

36 Raschetti R, Maggini M, Da Cas R, Popoli P. Time trends in the coprescribing of cisapride and contraindicated drugs in Umbria, Italy. J Am Med Assoc 2001 04;285(14):1840-1841.

37 Staniscia T, Romano F, Festi D, Bilker WB, Macones GA, Strom BL. Co-dispensing of contraindicated medications in patients using cisapride in Italy. Pharmacoepidemiol Drug Saf 2006 07;15(7):469-476.

38 De Bruin ML, Panneman MJM, Leufkens HGM, Hoes AW, Herings RMC. Use of cisapride with contraindicated drugs in the Netherlands. Ann Pharmacother 2002 36(2):338-343.

39 de la Porte M, Reith D, Tilyard M. Impact of safety alerts upon prescribing of cisapride to children in New Zealand. N Z Med J 2002 115(1157):U24.

40 Kurian BT, Ray WA, Arbogast PG, Fuchs DC, Dudley JA, Cooper WO. Effect of regulatory warnings on antidepressant prescribing for children and adolescents. Arch Pediatr Adolesc Med 2007 161(7):690-696.

41 Nemeroff CB, Kalali A, Keller MB, Charney DS, Lenderts SE, Cascade EF, et al. Impact of publicity concerning pediatric suicidality data on physician practice patterns in the United States. Arch Gen Psychiatry 2007 64(4):466-472.

42 Forrester MB. Selective serotonin re-uptake inhibitor warnings and trends in exposures reported to poison control centres in Texas. Public Health 2008 122(12):1356-1362.

43 Morrato EH, Libby AM, Orton HD, DeGruy III FV, Brent DA, Allen R, et al. Frequency of provider contact after FDA advisory on risk of pediatric suicidality with SSRIs. Am J Psychiatry 2008 165(1):42-50.

44 Singh T, Prakash A, Rais T, Kumari N. Decreased use of antidepressants in youth after US Food and Drug Administration black box warning. Psychiatry (USA) 2009 6(10):30-34.

45 Bergen H, Hawton K, Murphy E, Cooper J, Kapur N, Stalker C, et al. Trends in prescribing and self-poisoning in relation to UK regulatory authority warnings against use of SSRI antidepressants in under-18-year-olds. Br J Clin Pharmacol 2009 68(4):618-629.

46 Katz LY, Kozyrskyj AL, Prior HJ, Enns MW, Cox BJ, Sareen J. Effect of regulatory warnings on antidepressant prescription rates, use of health services and outcomes among children, adolescents and young adults. Can Med Assoc J 2008 178(8):1005-1011.

47 Kurdyak PA, Juurlink DN, Mamdani MM. The effect of antidepressant warnings on prescribing trends in Ontario, Canada. Am J Public Health 2007 97(4):750-754.

48 Dean AJ, Hendy A, McGuire T. Antidepressants in children and adolescents - Changes in utilisation after safety warnings. Pharmacoepidemiol Drug Saf 2007 16(9):1048-1053.

49 Libby AM, Brent DA, Morrato EH, Orton HD, Allen R, Valuck RJ. Decline in treatment of pediatric depression after FDA advisory on risk of suicidality with SSRIs. Am J Psychiatry 2007 164(6):884-891.

50 Carlson AM, Stockwell Morris L. Coprescription of terfenadine and erythromycin or ketoconazole: An assessment of potential harm. J Am Pharm Assoc 1996 36(4):263-269.

51 Thompson D, Oster G. Use of terfenadine and contraindicated drugs. J Am Med Assoc 1996 05;275(17):1339-1341.

52 Burkhart GA, Sevka MJ, Temple R, Honig PK. Temporal decline in filling prescriptions for terfenadine closely in time with those for either ketoconazole or erythromycin. Clin Pharmacol Ther 1997 61(1):93-96.
53 Cluxton Jr. RJ, Li Z, Heaton PC, Weiss SR, Zuckerman IH, Moomaw CJ, et al. Impact of regulatory labelling for troglitazone and rosiglitazone on hepatic enzyme monitoring compliance: Findings from the state of Ohio Medicaid program. Pharmacoepidemiol Drug Saf 2005 14(1):1-9.
54 Shatin D, Gardner JS, Stergachis A, Blough D, Graham D. Impact of mailed warning to prescribers on the co-prescription of tramadol and antidepressants. Pharmacoepidemiol Drug Saf 2005 14(3):149-154.
55 Shatin D, Rawson NSB, Curtis JR, Braun MM, Martin CK, Moreland LW, et al. Documented tuberculin skin testing among infliximab users following a multi-modal risk communication interventions. Pharmacoepidemiol Drug Saf 2006 15(1):11-18.
56 Willy ME, Manda B, Shatin D, Drinkard CR, Graham DJ. A Study of Compliance with FDA Recommendations for Pemoline (Cylert(registered trademark)). J Am Acad Child Adolesc Psychiatry 2002 41(7):785-790.
57 Gleason PP, Walters C, Heaton AH, Schafer JA. Telithromycin: The perils of hasty adoption and persistence of off-label prescribing. J Managed Care Pharm 2007 13(5):420-425.
58 Kazmierczak R, Coley KC. Impact of 'Dear Doctor' letters on prescribing: Evaluation of the use of tramadol HCl. Formulary 1997 32(9):968-978.
59 Wheeler BW, Metcalfe C, Gunnell D, Stephens P, Martin RM. Population impact of regulatory activity restricting prescribing of COX-2 inhibitors: Ecological study. Br J Clin Pharmacol 2009 68(5):752-764.
60 Malgarini RB, Pimpinella G. Thrombotic thrombocytopenic purpura induced by ticlopidine: The power of 'Dear Health Professional' letters. Ann Pharmacother 2000 34(3):404-405.
61 Motola D, Vargiu A, Leone R, Conforti A, Moretti U, Vaccheri A, et al. Influence of regulatory measures on the rate of spontaneous adverse drug reaction reporting in Italy. Drug Saf 2008 31(7):609-616.
62 Morera T, Gervasini G, Carrillo JA, Benitez J. Evaluation of a drug-drug interaction alert structure through the retrospective analysis of statins-macrolides co-prescriptions. Basic Clin Pharmacol Toxicol 2005 96(4):289-294.
63 Valiyeva E, Herrmann N, Rochon PA, Gill SS, Anderson GM. Effect of regulatory warnings on antipsychotic prescription rates among elderly patients with dementia: A population-based time-series analysis. CMAJ 2008 08;179(5):438-446.
64 Azoulay L, Oraichi D, Berard A. Patterns and utilization of isotretinoin for acne from 1984 to 2003: Is there need for concern? Eur J Clin Pharmacol 2006 08;62(8):667-674.
65 Graham DJ, Drinkard CR, Shatin D, Tsong Y, Burgess MJ. Liver enzyme monitoring in patients treated with troglitazone. J Am Med Assoc 2001 08;286(7):831-833.
66 Panorama. The secrets of Seroxat. BBC News. Available at: http://news.bbc.co.uk/2/hi/programmes/panorama/2310197.stm. Accessed February 10, 2011.
67 U.S. Food and Drug Administration. Historical information on antidepressant use in children, adolescents, and adults. 2010; Available at: http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm096293.htm. Accessed February 15, 2011.
68 Berry DC, Raynor DK, Knapp P, Bersellini E. Official warnings on thromboembolism risk with oral contraceptives fail to inform users adequately. Contraception 2002 11;66(5):305-307.

69 Ramsay C, Brown E, Hartman G, Davey P. Room for improvement: A systematic review of the quality of evaluations of interventions to improve hospital antibiotic prescribing. J Antimicrob Chemother 2003 52(5):764-771.

70 Lu CY, Ross-Degnan D, Soumerai SB, Pearson SA. Interventions designed to improve the quality and efficiency of medication use in managed care: a critical review of the literature - 2001-2007. BMC Health Serv Res 2008 8(1):75.

71 Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther 2002 27(4):299-309.

Appendix table. Key criteria of included studies

Author	Country	Study design	Quality score	Assessed warning	Intended		Unintended	
					Outcome measure	Effect[a]	Outcome measure	Effect[a]
SSRIS –Suicidality and suicidal thoughts								
Bergen et al. (2009) (45)	UK	ITS	7/8	DHPC Dec 2003 UK	Drug use	+	Other (self-poisoning)	+
Dean et al. (2007) (48)	Australia	ITS	5/8	DHPC Jun 2003 UK	Drug use	+		
Forrester (2008) (42)	USA	ITS	6/8	DHPC Jan 2002 US; PHA Jun 2003 US; PHA Oct 2003 US; PHA Feb/Mar 2004 US; BBW Sept/Oct 2004 US; DHPC Sept 2005 US; DHPC Dec 2005 US; PHA Dec 2005 US			Other (self-poisoning)	Overall[D]: +
Gibbons et al. (2007) (12)	USA & Netherlands	BA	5/6	PHA Oct 2003 US; DHPC Dec 2003 UK; DHPC Dec 2003 EU; PHA Feb/Mar 2004 US; BBW Sept/Oct 2004 US; BBW Dec 2006 US	Drug use	Overall[D]: +	Other (suicide rates) Drug use (adults spill over)	Overall[D]: + Overall[D]: +
Katz et al. (2008) (46)	Canada	BA	5/6	PHA Jun 2004 Canada	Drug use	+	Other (suicide rates) Care (health services use)	+ +
Kurdyak et al. (2007) (47)	Canada	ITS	6/8	DHPC Jun 2003 UK; PHA Oct 2003 US; PHA Feb/Mar 2004 US; PHA Jun 2004 Canada; BBW Sept/Oct 2004 US	Drug use	DHPC Jun 2003 UK: -; PHA Oct 2003 US: +; PHA Feb/Mar 2004 US: -; PHA Jun 2004 Canada: -; BBW Sept/Oct 2004 US:-		
Kurian et al. (2007) (40)	USA	ITS	7/8	DHPC Dec 2003 UK; BBW Sept/Oct 2004 US	Drug use	DHPC Dec 2003 UK: +; BBW Sept/Oct 2004 US: -		

Appendix table. Continued

Author	Country	Study design	Quality score	Assessed warning	Intended		Unintended	
					Outcome measure	Effect[a]	Outcome measure	Effect[a]
Libby et al. (2007) (49)	USA	ITS & BA	7/8	PHA Oct 2003 US	Drug use (ITS) Care (diagnosing patterns: Paediatric) (BA)	+ +	Drug use (alternatives)	-
Morrato et al. (2008) (43)	USA	ITS	6/8	PHA Oct 2003 US	Care (treatment monitoring)	-		
Murray et al (2005) (11)	UK	BA	5/6	DHPC Dec 2003 UK	Drug use	+		
Nemeroff et al. (2007) (41)	USA	ITS	6/8	PHA Oct 2003 US; PHA Feb/Mar 2004 US; BBW Sept/Oct 2004 US	Drug use Care (prescriber specialty)	PHA Oct 2003 US: -; PHA Feb/Mar 2004 US: +; BBW Sept/Oct 2004 US: + PHA Oct 2003 US: +; PHA Feb/Mar 2004 US: +; BBW Sept/Oct 2004 US: +		
Olfson et al. (2008) (14)	USA	ITS	7/8	PHA Jun 2003 US; BBW Sept/Oct 2004 US	Drug use	PHA Jun 2003 US: +; BBW Sept/Oct 2004 US: -	Drug use (adults spill over)	Overall[D]: +
Singh et al (2009) (44)	USA	BA	5/6	BBW Sept/Oct 2004 US	Other (refusal of Rx)	+		
Valuck et al. (2007) (13)	USA	ITS	7/8	PHA Oct 2003 US	Care (diagnosing patterns: Adults)	+	Drug use (adults 'spill over effect')	+
Wheeler et al. (2008) (15)	UK	BA	5/6	DHPC Jun 2003 UK; DHPC Dec 2003 UK	Drug use	Overall[D]: +	Other (suicide rates) Care (hospital admissions)	Overall[D]: - Overall[D]: -
Third Generation Oral Contraceptives – Venous thromboembolism								
Child et al. (1996) (23)	UK	BA	4/6	DHPC Oct 1995 UK			Other (abortions)	+

Appendix table. Continued

Author	Country	Study design	Quality score	Assessed warning	Intended		Unintended	
					Outcome measure	Effect[a]	Outcome measure	Effect[a]
Farmer et al. (2000) (28)	UK	ITS & BA	7/8	DHPC Oct 1995 UK	Drug use (BA) Other (VTE cases) (ITS)	+ -		
Ferguson et al. (1996) (24)	UK	BA	4/6	DHPC Oct 1995 UK	Drug use	+		
Martin et al. (1997) (25)	UK	BA	5/6	DHPC Oct 1995 UK	Drug use Other (discontinuation. rates / switches)	+ -		
Roberts et al. (1997) (26)	UK	BA	4/6	DHPC Oct 1995 UK	Drug use	+		
Skjeldestad et al. (1997) (29)	Norway	BA	4/6	DHPC Oct 1995 UK	Drug use	+	Other (abortions)	+
De Vries et al. (1998) (31)	Netherlands	BA	5/6	DHPC Oct 1995 UK	Drug use	+		
Williams et al. (1998) (30)	Ireland	ITS	4/8	DHPC Oct 1995 UK			Drug use	+
Wood et al. (1997) (27)	UK	BA	5/6	DHPC Oct 1995 UK			Other (conceptions)	+
Cisapride – Cardiac arrhythmias/prolonged QT interval, with concurrent CYP3A4 inhibitor use								
De Bruin et al. (2002) (38)	Netherlands	BA	5/6	DHPC Oct 1995 NL	CI use / DDI	+		
De la Porte et al. (2002) (39)	New Zealand	ITS	5/8	DHPC Nov 2000 NZ	Drug use	+		

Appendix table. Continued

Author	Country	Study design	Quality score	Assessed warning	Intended		Unintended	
					Outcome measure	Effect[a]	Outcome measure	Effect[a]
Guo et al. (2003) (32)	USA	ITS	7/8	DHPC Feb 1995 US; DHPC Oct 1995 US; DHPC Jun 1998 US	CI use / DDI	DHPC Feb 1995 US: -; DHPC Oct 1995 US: -; DHPC Jun 1998 US: +		
Jones et al. (2001) (34)	USA	ITS	3/8	DHPC Oct 1995 US; DHPC Jun 1998 US	CI use / DDI	DHPC Oct 1995 US: -; DHPC Jun 1998 US: -		
Raschetti et al. (2001) (36)	Italy	BA	4/6	DHPC 1998 Italian	CI use / DDI, Drug use	- -		
Smalley et al. (2000) (33)	USA	BA	5/6	DHPC Jun 1998 US	CI use / DDI	-		
Staniscia et al. (2006) (37)	Italy	BA	5/6	DHPC 1998 Italian	CI use / DDI	-		
Weatherby et al. (2001) (35)	USA	ITS	6/8	DHPC Oct 1995 US; DHPC Jun 1998 US	CI use / DDI	DHPC Oct 1995 US: -; DHPC Jun 1998 US: +		
Wilkinson et al. (2004) (21)[B]	USA	ITS	6/8	DHPC Feb 1995 US; DHPC Oct 1995 US; DHPC Jun 1998 US; DHPC Jun 1999 US; DHPC Jan 2000 US	Drug use - overall	 DHPC Feb 1995 US: -; DHPC Oct 1995 US: -; DHPC Jun 1998 US: +; DHPC Jun 1999 US: +; DHPC Jan 2000 US: +		
					-new users	DHPC Feb 1995 US: -; DHPC Oct 1995 US: +; DHPC Jun 1998 US: +; DHPC Jun 1999 US: +; DHPC Jan 2000 US: +		
Terfenadine – Cardiac arrhythmias/prolonged QT interval, with concurrent CYP3A4 inhibitor use								
Burkhart et al. (1997) (52)	USA	ITS	4/8	DHPC Jul 1992 US	CI use / DDI	+		

Appendix table. Continued

Author	Country	Study design	Quality score	Assessed warning	Intended		Unintended	
					Outcome measure	Effect[a]	Outcome measure	Effect[a]
Carlson et al. (1996) (50)	USA	BA	4/6	DHPC Aug 1990 US, BBW Jul 1992 US	CI use / DDI - with erythromycin - with ketoconazole	 Overall[D]: + Overall[D]: -		
Thompson et al. (1996) (51)	USA	ITS	6/8	DHPC Aug 1990 US, BBW Jul 1992 US	CI use / DDI	Overall[D]: +		
Troglitazone – Hepatoxicity								
Cluxton et al. (2005) (53)	USA	BA	5/6	DHPC Jul 1998 US, DHPC Jun 1999 US	Lab testing	Overall[D]: +		
Graham et al. (2001) (65)	USA	BA	5/6	DHPC Oct 1997 US, DHPC Dec 1997 US, DHPC Jul 1998 US, DHPC Jun 1999 US	Lab testing	Overall[D]: +		
Wilkinson et al. (2004) (21)[B]	USA	ITS	6/8	DHPC Oct 1997 US, DHPC Dec 1997 US, DHPC Jul 1998 US, DHPC Jun 1999 US	Drug use -overall -new users	 DHPC Oct 1997 US: -; DHPC Dec 1997 US: -; DHPC Jul 1998 US: -; DHPC Jun 1999 US: - DHPC Oct 1997 US: +; DHPC Dec 1997 US: +; DHPC Jul 1998 US: +; DHPC Jun 1999 US: +		
Tramadol – Seizures								
Kazmierczak et al. (1997) (58)	USA	BA	4/6	DHPC Mar/Apr 1996 US	CI use / DDI	-		
Shatin et al. (2005) (54)	USA	ITS	6/8	DHPC Mar/Apr 1996 US	CI use / DDI	-		

Appendix table. Continued

Author	Country	Study design	Quality score	Assessed warning	Intended		Unintended	
					Outcome measure	Effect[a]	Outcome measure	Effect[a]
Other								
Azoulay et al. (2006) (64) Isotretinoin - Teratogenicity and psychiatric risks	Canada	ITS	7/8	DHPC Jan 2001 Canadian	Drug use	-		
Gleason et al. (2007) (57) Telithromycin – Hepatoxicity	USA	ITS	5/8	BBW Feb 2007 US	Drug use CI use/DDI	+ -		
Malgarini et al. (2000) (60) Ticlopidine – Thrombotic Thrombocytopenic Purpura	Italy	BA	3/6	DHPC Apr 1998 Italian	Spontaneous ADE reporting	+		
Morera et al. (2005) (62) Statins – Rhabdomyloysis risk with concurrent CYP3A4 inhibitors use	Spain	BA	5/6	DHPC Jun 2001 Spanish DHPC Jul 2001 Spanish	CI use / DDI	Overall[D]: -		
Motola et al. (2008) (61) Nimesulide – Hepatoxicity	Italy	ITS	4/8	DHPC 2002 Italian	Spontaneous ADE reporting	+		
Shatin et al. (2006) (55) Infliximab – Tuberculosis	USA	BA	5/6	DHPC Oct 2001 US BBW Oct 2001 US	Lab testing	Overall[D]: +		

Appendix table. Continued

Author	Country	Study design	Quality score	Assessed warning	Intended		Unintended	
					Outcome measure	Effect[a]	Outcome measure	Effect[a]
Starner et al. (2008) (22)[C] Rosiglitazone – Cardiac ischemic events	USA	ITS & BA	5/8	BBW Aug 2007 US	Drug use (ITS) CI use/DDI (BA)	Overall[D]: + Overall[D]: +		
Starner et al. (2008) (22)[C] Pioglitazone – Cardiac ischemic events	USA	ITS & BA	5/8	BBW Aug 2007 US	Drug use (ITS) CI use/DDI (BA)	Overall[D]: + Overall[D]: +		
Valiyeva et al. (2008) (63) Antipsychotics – Cerebrovascular events	Canada	ITS	5/8	DHPC Oct 2002 Canadian DHPC Mar 2004 Canadian DHPC Jun 2005 Canadian	Drug use	All: +		
Willy et al. (2002) (56) Pemoline - Hepatoxicity	USA	ITS	6/8	DHPC Dec 1996 US BBW Dec 1996 US DHPC Jun 1999 US	Lab testing Drug use	Overall[D]: - Overall[D]: +		
Wheeler et al (2009) (59) Cox-2 inhibitors – Cardiovascular risk	UK	ITS	6/8	PHA Sept 2001 US DHPC Dec 2004 UK	Other (mortality) Care (hospital admission) Drug use	Overall[D]: - Overall[D]: - Overall[D]: +		

+ = Effect; - = No effect; [A] Effect according to author(s). [B] Paper Wilkinson et al. (2004) appears both in categories CISAPRIDE & TROGLITAZONE. [C] Paper Starner et al. (2008) appears twice in category OTHER. [D] Overall [effect] indicates the impact of all mentioned safety warnings are evaluated as a whole in the study.
SSRI = Selective serotonin reuptake inhibitors; **UK** = United Kingdom; **ITS** = Interrupted Time Series; **USA** = United States of America; **BA** = Before/after study or ITS with less than 3 data points before or after an intervention; **VTE** = Venous Thromboembolism; **NL** = The Netherlands; **NZ** = New Zealand; CI**/DDI** = Contraindicated use/Drug-Drug Interaction; **DHPC** = Direct Healthcare Professional Communication; **BBW** = Black Box Warning; **PHA** = Public Health Advisory.

Chapter 3

Impact of safety-related regulatory action on drug use in ambulatory care in the Netherlands.

Sigrid Piening[1]*
Katrin C. Reber[2]*
Jaap E. Wieringa[2]
Sabine M.J.M. Straus[3,4]
Pieter A. de Graeff[1,3]
Flora M. Haaijer-Ruskamp[1]
Peter G.M. Mol[1,3]

*The first two authors contributed equally

Clinical Pharmacology & Therapeutics 2012 91:5 (838-845)

[1]Department of Clinical Pharmacology, Graduate School of Medical Sciences, University Medical Center Groningen, University of Groningen, the Netherlands
[2]Department of Marketing, University of Groningen, Groningen, the Netherlands
[3]Dutch Medicines Evaluation Board, Utrecht, the Netherlands
[4]Department of Medical Informatics, Erasmus Medical Center, Rotterdam, the Netherlands

Abstract

The effect of Direct Healthcare Professional Communications (DHPCs) informing healthcare professionals of serious drug safety issues has been questioned. The aim of this study was to evaluate the impact of DHPCs on drug use. Nationwide dispensing data for the period 2000–2008 for new users of 46 drugs with one or more DHPCs were assessed. Impact on short-term volume of use was evaluated with regression models, and the presence of long-term changes in use was evaluated with interrupted time series analyses incorporating pre-existing trends. The short-term prescription level was lower post-DHPC in 28 (48.3%) of 58 cases. Twenty (34.5%) DHPCs resulted in long-term changes in use. A long-term mean reduction in use was observed in 26.7% of cases (95% confidence interval, −15.2 to −38.2%). Long-term changes in use were not significantly related to pre-existing trends in use. Although short- and long-term decreases in use were observed after only half and a third of DHPCs, respectively, the decrease was substantial.

Introduction

At market entry, the safety profile of a new drug is not fully known because of inherent shortcomings of preregistration clinical trials, such as small sample sizes, focus on efficacy, and inclusion of relatively healthy patient groups.[1,2] For ~10% of all drugs, new and serious safety issues are identified after market approval, necessitating safety-related regulatory action.[3-5] These safety issues can emerge not only shortly after market entry but also at a later stage in the drug's life cycle.[3-5] Occasionally, the benefits of a drug no longer outweigh its risks, leading to its withdrawal from the market. For example, rimonabant, an anti-obesity drug, was withdrawn in 2009 because of safety concerns at an early stage of its life cycle (<3 years after market approval). Similarly, rosiglitazone, a drug used to treat diabetes, was withdrawn in 2010 because of safety concerns at a more mature stage (>10 years after market approval).[6,7] On-going post-registration benefit–risk evaluation and, when indicated, safety-related regulatory action are required to safeguard a positive balance of benefits over risks of individual drugs. To this end, risk-management plans became mandatory in the European Union in 2005.[8]

Prescribing trends of drugs presumably show an initial increase in prescription rates, after which they level out, and at a later stage in the life cycle they decrease.[9] One would expect safety-related regulatory action to have dissimilar impact, depending on when in the drug's life cycle it is taken. However, such information is currently not available.

Communication of important new safety issues in the European Union is currently primarily performed by sending paper-based warning letters to health-care professionals; these are called Direct Healthcare Professional Communications (DHPCs or 'Dear Doctor letters'). DHPCs in the European Union are defined as information aimed at ensuring safe and effective use of medicinal products.[10] In recent years, the effectiveness of these warning letters has been questioned.[11-13] The impact of safety-related regulatory action was evaluated mainly for third generation oral contraceptives, cisapride, and selective serotonin reuptake inhibitors.[14-19] The small number of drug groups, often weak study designs, and differences in outcome measures hamper drawing conclusions on effect sizes of safety-related regulatory action. Information about the impact of DHPCs is particularly relevant because evaluating the outcome of risk minimization will become mandatory in the near future and a point of reference is needed.[20,21]

The aim of this study was to evaluate the impact of DHPCs on drug use in the Netherlands, taking into account pre-existing prescribing trends.

Methods

Design

In this longitudinal study, all drugs for which a DHPC was issued between January 2001 and January 2008 in the Netherlands were included. We excluded drugs that were not dispensed in ambulatory care, drugs that had insufficient dispensing data (≤10 prescriptions/month pre- and post-DHPC), and drugs for which a market withdrawal was announced in the DHPC. New drug use (defined as number of new prescriptions per drug and no dispensing to the patient in the previous 6 months) was selected as main outcome measure to assess the impact of DHPCs. The following drug and DHPC characteristics were retrieved: International Non-proprietary Names, ATC classification, registration date, date of DHPC, time from registration to DHPC, and safety issue (including System Organ Class).

Data

Monthly dispensing data for the period 2000–2008 were obtained from the Dutch Foundation for Pharmaceutical Statistics database. This database comprises drug dispensing data of about 90% (15 million) of the Dutch population.[22] DHPCs were collected from the Dutch Healthcare Inspectorate paper archive and the website of the Dutch Medicines Evaluation Board.[23] The drug and DHPC characteristics were retrieved from the DHPCs, the Database Human Medicines of the Dutch Medicines Evaluation Board,[24] the World Health Organization ATC classification system,[25] and the Medical Dictionary for Regulatory Activities.

Analyses

The DHPC was used as the unit of analysis. We first evaluated the impact of DHPCs on short-term volume of drug use using regression models. Second, we determined whether a DHPC led to a long-term change in use with interrupted time series analyses. Short-term changes in use were defined as a significant increase, no change, or a significant decrease in prescription rates. Two aspects of change were identified: changes in average use (i.e., level) and trends in use (i.e., slopes) before and after the DHPC. Per DHPC, we computed trend regression models for the periods 12 months before and 12 months after the DHPC. A pooled (two-sample) t-test was used to determine whether the intercept estimates for the pre- and post- DHPC period were significantly different from each other. To consider all possible combinations in trend before and after the DHPC, we tested whether the estimates of the slope coefficient (for the pre- and post-DHPC period) were significantly different from zero, negative, or positive. For that purpose, we performed standard t-tests. P values of ≤0.05 were considered statistically significant. We used an interrupted

time series design based on the autoregressive integrated moving average modelling approach[26,27] to analyse the size and significance of long-term changes in use during the total study period associated with the DHPC for each drug included. Long-term changes indicate a change in the level of use from the time of the DHPC until the end of our observational period. Safety-related regulatory action in the form of a DHPC is included in the model as an intervention that may interrupt the normal course of the use of a drug. We expected a DHPC to have a sudden (rather than gradual) effect on drug use; therefore, we modelled the intervention as an abrupt change at the time of the DHPC that will have a permanent effect on drug use. The DHPC was included as a dummy variable taking the value 0 in the pre-intervention period and the value 1 at the time of intervention and thereafter. Because a DHPC could have been surrounded by premonition (e.g., scientific articles, communication circulated by healthcare professionals) or issued at the end of a month, we also allowed for a lead (i.e., the month before the issuance month) or delayed effect (i.e., 1 or 2 months after the DHPC) of the DHPC on the prescription series. We determined an appropriate time series regression model that accounts for any (systematic) variation that is independent of the intervention. Plots of the raw data and the (partial) autocorrelation function were used to identify non-stationarity. In addition, unit root tests were applied. If non-stationarity was present, we transformed the series by taking first differences to yield a stationary series. On the basis of the partial autocorrelation function, we determined the order of the autoregressive and moving average components. Both seasonal fluctuations and trends were taken into account. The model with the best fit and adequate diagnostic statistics was chosen according to Akaike and Schwarz information criteria.[28,29] Residuals were computed for diagnostic checks. To assess the impact of the intervention, the intervention term was inserted into the previously determined time series model. Changes in the level of prescribing (drug use) related to the intervention were considered statistically significant when $p \leq 0.05$. The analyses were performed separately for each drug. When two DHPCs were issued close in time, they were treated as a single intervention and analysed together. In such a case, the date of issuance of the first DHPC was taken as the time point of intervention. To make the size of the impact comparable across drugs, we calculated standardized effect sizes by dividing the effect size by the median drug use in the 12 months before the intervention. Chi-square tests were used to assess associations between pre-existing trends and long-term changes in use.

Results

A total of 120 DHPCs were issued in the Netherlands during the study period. Sixty-one DHPCs were excluded from further analysis: 38 DHPCs were issued for drugs solely used in

hospital settings, 18 DHPCs were issued for drugs with fewer than (median) 10 drug users per month over the entire study period, and five DHPCs were issued for drugs that were withdrawn from the market. As a result, 59 DHPCs were included for 46 drug groups covering 11 of 14 Anatomical Therapeutic Chemical (ATC) groups (level 1) (**Table 1**). The impact of two DHPCs, both issued for nelfinavir 1 month apart, could not be evaluated separately and were therefore analysed as one, leading to a total of 58 DHPCs to be analysed for 46 drugs. DHPCs were issued after a mean of 9.67 (SD 8.3) years after registration ('time from registration to DHPC'). In the 12-month (baseline) period preceding the DHPC, the median number of users of the included drugs ranged from 7 (sirolimus) to 53,596 (salbutamol) (**Table 1**).

Short-term changes in volume of use

Half (29) of all DHPCs were issued for drugs without any significant change in pre-existent trends (slope) in use, 13 were issued for drugs whose use was decreasing, and 16 for drugs whose use was increasing in the 12-month period before the DHPC was issued (**Table 2**). The short-term level of prescribing was lower after the DHPC for half (28) of the drugs and evenly distributed across the unchanged (14) or higher (16) categories for the other half of the drugs. Three clusters in short-term changes in use exist. The first cluster consists of 11 of 13 drugs with decreasing use before the DHPC that continued to decrease or levelled off after the DHPC, but at a lower level than before the DHPC. A second cluster consists of 21 of 29 drugs with unchanged slope coefficients before and after the DHPC and with no changes in levels of use. The third cluster consists of eight drugs for which pre-existent increasing use levels off after the DHPC but at a higher level than before the DHPC.

Long-term changes in volume of use

Forty-six interrupted time series models were developed to evaluate any long-term change in number of prescriptions after (58) individual DHPCs were issued for the 46 drugs (descriptions of individual models are available upon request). Twenty (34.5%) DHPCs resulted in a long-term change in drug use (**Table 1**). For these 20 DHPCs, the mean use decreased by 26.7% (95% confidence interval, −15.21 to −38.19%). A long-term increase in use (+15.4%; 95% confidence interval, 3.74 to 27.06%) was observed after the DHPC for lopinavir/ritonavir (**Figure 1**).

Long-term changes in volume of use in relation to pre-existing trends in use

Significant long-term changes were seen in 8 of 13 (62%) drugs with a pre-existing decreasing trend in use (cisapride[1], itraconazole, piroxicam, rosiglitazone[2], didanosine, leflunomide, desogestrel + ethinylestradiol (EE), and gestodene + EE), in 8 of 29 (28%)

Table 1. Characteristics of DHPCs with and without long term impact on drug use.

INN (ATC)	Approval date	DHPC date	Safety issue (SOC)	Median (no. of Rx 12 month pre-DHPC)	Standardized effect size	P-value	No. of observations (used for analysis)
DHPCs with significant long-term changes in use							
cisapride (A03FA02)	Jul-88	Sep-02	Electrocardiogram QT prolonged (Investigations)	4148.5	-0.433	0.000	108
rosiglitazone (A10BG02)	Jul-00	Jan-06	Macular oedema (Eye)	1488	-0.327	0.000	108
		Mar-07	Fracture (Musculoskeletal)	964	-0.637	0.000	108
pioglitazone (A10BG03)	Oct-00	Apr-07	Fracture (Musculoskeletal)	1012	-0.320	0.005	84
desogestrel and EE (G03AA09)	May-81	Sep-01	Venous thrombosis (Vascular)	10605	-0.153	0.001	108
gestodene and EE (G03AA10)	May-89	Sep-01	Venous thrombosis (Vascular)	5719.5	-0.208	0.000	108
itraconazole (J02AC02)	Oct-90	May-01	Cardiac failure (Cardiac)	8834.5	-0.097	0.006	108
lopinavir/ ritonavir (J05AE06)	Mar-01	Sep-06	Circumstance or information capable of leading to medication error (Injury)	94.5	0.154	0.011	89
didanosine (J05AF02)	Aug-00	Mar-05	Drug effect decreased (General)	40.5	-0.438	0.002	108
leflunomide (L04AA13)	Sep-99	Mar-01	Hepatitis (Hepatobiliary)	432	-0.315	0.000	108
piroxicam (M01AC01)	Jun-87	Aug-07	Gastrointestinal disorder (Gastrointestinal)	2920.5	-0.494	0.000	108
celecoxib (M01AH01)	May-00	Dec-04	Cardiovascular disorder (Cardiac)	11851.5	-0.570	0.000	72
etoricoxib (M01AH05)	Jul-02	Feb-05	Cardiovascular disorder (Cardiac)	12375.5	-0.153	0.006	68
strontium ranelate (M05BX03)	Sep-04	Nov-07	Drug rash with eosinophilia and systemic symptoms: DRESS (Blood)	344.5	-0.674	0.000	41
vigabatrine (N03AG04)	Sep-90	Sep-02	Visual field defect (Nervous)	40	-0.186	0.007	108
lamotrigine (N03AX09)	Jan-96	Jun-06	Maternal drugs affecting foetus (Injury)	746	-0.155	0.001	108
pergolide (N04BC02)	Jul-91	Apr-05	Cardiac valve disease (Cardiac)	142	-0.245	0.008	108
olanzapine (N05AH03)	Sep-96	Mar-04	Death (General)	2193	-0.171	0.009	70
paroxetine (N06AB05)	Jun-91	Mar-06	Maternal drugs affecting foetus (Injury)	10613	-0.145	0.044	67
bupropion (N06AX12)	Dec-99	May-01	Convulsion	4399.5	-0.406	0.000	108
DHPCs without significant long-term changes in use							
cisapride (A03FA02)	Jul-88	Sep-04	Electrocardiogram QT prolonged (Investigations)	408.5	0.155	0.880	108
sibutramine (A08AA10)	Apr-01	Jul-02	Cardiovascular disorder (Cardiac)	567.5	0.001	0.998	92
repaglinide (A10BX02)	Aug-98	May-03	Hypoglycaemia (Endocrine)	47.5	-0.193	0.283	108

Table 1. Continued

INN (ATC)	Approval date	DHPC date	Safety issue (SOC)	Median (no. of Rx 12 month pre-DHPC)	Standardized effect size	P-value	No. of observations (used for analysis)
epoetine alfa (B03XA01)	Nov-88	Nov-01	Aplasia pure red cell (Blood)	417	0.078	0.563	108
epoetine alfa (B03XA01)	Nov-88	Jul-02	Aplasia pure red cell (Blood)	495.5	0.201	0.076	108
epoetine alfa (B03XA01)	Nov-88	Dec-02	Aplasia pure red cell (Blood)	551.5	-0.114	0.256	108
rosuvastatine (C10AA07)	Nov-02	Jun-04	Rhabdomyolysis (Musculoskeletal)	5968.5	0.122	0.312	70
gemfibrozil (C10AB04)	Jul-90	May-03	Hypoglycaemia (Endocrine)	595	0.029	0.747	108
tacrolimus (D11AX14)	Apr-96	Apr-06	Lymphoma (Blood)	1550.5	-0.199	0.147	108
pimecrolimus (D11AX15)	Apr-03	Apr-06	Lymphoma (Blood)	913.5	-0.074	0.513	67
hormone suppletion therapy (G03F)	Jul-76	Dec-03	Breast cancer (Neoplasms)	2951	0.104	0.375	108
tamsulosine (G04CA02)	Apr-95	Aug-06	Floppy iris syndrome (Nervous)	6142	0.016	0.749	108
somatropin (H01AC01)	Nov-91	Jun-07	Circumstance or information capable of leading to medication error (Injury)	116.5	-0.144	0.180	108
triamcinolon acetonide (H02AB08)	Sep-66	Dec-06	Eye disorder (Eye)	11643.5	-0.091	0.225	108
nelfinavir (J05AE04)	Jan-98	Jun-07 & Jul-07[a]	Therapeutic product contamination (Injury)	15	-0.139	0.561	108
lopinavir/ ritonavir (J05AE06)	Mar-01	Aug-07	Incorrect dose administered (Injury)	109.5	0.036	0.476	89
stavudine (J05AF04)	May-96	Sep-01	Muscular weakness (Nervous)	73.5	-0.045	0.580	108
tenofovir (J05AF07)	Feb-02	Jul-03	Drug effect decreased (General)	97.5	0.206	0.324	74
tenofovir (J05AF07)	Feb-02	Oct-03	Drug effect decreased (General)	97.5	-0.284	0.176	74
tenofovir (J05AF07)	Feb-02	Mar-05	Drug effect decreased (General)	137	-0.010	0.947	74
tenofovir (J05AF07)	Feb-02	Mar-06	Renal disorder (Renal)	167.5	0.163	0.183	74
nevirapine (J05AG01)	Feb-98	Feb-04	Skin reaction (Skin)	86.5	0.035	0.679	108
imatinib mesilate (L01XE01)	Nov-01	Mar-05	Urinary bladder adenoma (Renal)	37.5	0.188	0.320	60
imatinib mesilate (L01XE01)	Nov-01	Dec-06	Cardiac failure (Cardiac)	53.5	-0.197	0.175	60
Hydroxycarba-mide (L01XX05)	Nov-72	Dec-05	Cutaneous vasculitis (Skin)	133	0.047	0.212	108
letrozol (L02BG04)	Jan-97	Dec-05	Maternal drugs affecting foetus (Injury)	240.5	0.139	0.089	108

Table 1. Continued

INN (ATC)	Approval date	DHPC date	Safety issue (SOC)	Median (no. of Rx 12 month pre-DHPC)	Standardized effect size	P-value	No. of observations (used for analysis)
mycophenolate mofetil (L04AA06)	Feb-96	Nov-07	Maternal drugs affecting foetus (Injury)	274	-0.028	0.602	108
sirolimus (L04AA10)	Mar-01	Feb-03	Bronchial anastomosis complication (Respiratory)	6.5	0.717	0.084	94
etanercept (L04AB01)	Feb-00	Feb-03	Infection (Infections)	28	-0.041	0.961	108
celecoxib (M01AH01)	May-00	Feb-05	Cardiovascular disorder (Cardiac)	11851.5	0.037	0.582	72
botuline a toxin (M03AX01)	Dec-93	Jun-07	Muscular weakness (Nervous)	25	-0.030	0.883	108
lamotrigine (N03AX09)	Jan-96	Oct-05	Drug effect decreased (General)	688	0.075	0.152	108
topiramate (N03AX11)	Jun-99	Oct-01	Oculomucocutaneous syndrome (Eye)	142	-0.048	0.868	108
levetiracetam (N03AX14)	Sep-00	Nov-07	Incorrect dose administered (Injury)	701	0.055	0.087	86
paroxetine (N06AB05)	Jun-91	Jan-06	Maternal drugs affecting foetus (Injury)	10451	0.041	0.658	108
venlafaxine (N06AX16)	Dec-97	Sep-03	Suicidal ideation (Psychiatric)	4222.5	0.105	0.128	108
galantamine (N06DA04)	Jul-03	Oct-05	Death (General)	232	-0.075	0.559	61
salbutamol (R03AC02)	Dec-73	May-07	Myocardial ischaemia (Cardiac)	53595.5	-0.114	0.105	108

a The two DHPCs issued for nelfinavir were issued close in time and were therefore treated as a single intervention and analysed together. The first DHPC was taken as the time point of intervention.
ATC= Anatomical Therapeutic Chemical; **DHPC=** Direct Healthcare Professional Communication; **DRESS=** Drug Rash Eosinophilia Systemic Symptoms; **EE=** ethinylestradiol; **INN=** International Proprietary Name; **MedRA=** Medical Dictionary for Regulatory Activities; **Rx=** Medical prescription; **SOC:** System Organ Class. **System Organ Class according to MedRA: Investigations**: Investigations; **Eye**: Eye disorders; **Musculoskeletal**: Muscoloskeletal and connective tissue disorders; **Vascular**: Vascular disorders; **Cardiac**: Cardiac disorders; **Injury**: Injury, poisoning and procedural complications; **General**: General disorders and administration site conditions; **Hepatobiliary**: Hepatobiliary disorders; **Gastrointestinal**: Gastrointestinal disorders; **Blood**: Blood and lymphatic system disorders; **Nervous**: Nervous system disorders; **Endocrine**: Endocrine disorders; **Neoplasms**: Neoplasms benign, malignant and unspecified (including cysts and polyps); **Renal**: Renal and urinary disorders; **Skin**: Skin and subcutaneous tissue disorders; **Respiratory**: Respiratory, thoracic and mediastinal disorders; **Infections**: Infections and infestations; **Psychiatric**: Psychiatric disorders

drugs with a stable (no significant increase or decrease) pre-existing trend (etoricoxib, rosiglitazone[1], bupropion, lamotrigine[2], pergolide, pioglitazone, vigabatrin, and lopinavir + ritonavir), and in 4 of 16 (25%) drugs with a pre-existing increasing trend (celecoxib[1], paroxetine[2], strontium ranelate, and olanzapine) (**Table 2;** drugs with more than one DHPC are indicated here by superscript numbers). However, no significant association was found between pre-existing trends in use and significant long-term changes (χ^2=5.46; P=0.065).

Table 2. Short-term changes in drug use pre and post DHPC (N=58).

Changes in trend*		Changes in level#		
Pre-DHPC	Post-DHPC	Lower (n=28)	Unchanged (n=14)	Higher (n=16)
Decrease (-) (n=13)	-	cisapride[1], cisapride[2], itraconazole, piroxicam, rosiglitazone[2]	-	-
	0	didanosine, gemfibrozil, HRT, leflunomide, desogestrel+EE, gestodene+EE	tenofovir[1]	-
	+	pimecrolimus	-	-
Unchanged (0) (n=29)	-	celecoxib[2], etoricoxib, rosiglitazone[1], stavudine	paroxetine[1]	-
	0	bupropion, lamotrigine[2], nelfinavir[1+2], pergolide, pioglitazone, repaglinide, somatropin, vigabatrine	hydroxycarbamide, imatinib mesilate[2], lopinavir+ritonavir[2], mycophenolate mofetil, nevirapine, rosuvastatin, salbutamol, triamcinolon acetonide	lopinavir+ritonavir[1], sirolimus, tamsulosine, topiramate, venlafaxine
	+	-	tacrolimus	sibutramine, tenofovir[3]
Increase (+) (n=16)	-	celecoxib[1]	tenofovir[4]	-
	0	paroxetine[2]	olanzapine	epoetine alfa[2], galantamine, imatinib mesilate[1], lamotrigine[1], letrozole, levetiracetam
	+	botuline A toxin, strontium ranelate	epoetine alfa[3]	epoetine alfa[1], etanercept, tenofovir[2]

Drugs with more than one DHPC are indicated by their superscript numbers. **a** Short-term changes in trend 12 months pre and post-DHPC, are indicated by 'decrease (-)' or, 'increase (+)' ($p<0.05$), or by 'unchanged (0)' ($p\geq0.05$). **b** Short-term changes in mean level 12 months post-DHPC compared to 12 months pre-DHPC, are indicated by 'lower' or 'higher' ($p<0.05$) or unchanged ($p\geq0.05$). **Example:** cisapride[1] situated in the upper left cell, indicates that before the first DHPC of cisapride its short-term use was decreasing (changes in trend pre-DHPC) and continued to decrease after (post-DHPC) the DHPC. In addition, the level of use was lower after the DHPC.
DHPC: Direct Healthcare Professional Communication; **EE**: Ethinylestradiol; **HRT**: Hormone Replacement Therapy.

Almost all (18 of 20) DHPCs leading to long-term changes in drug use had a lower level of use in the short term (12 months), whereas the DHPC for lopinavir/ritonavir (reporting a switch from capsule to tablet formulation) showed both a long-term increase in use and a higher use in the short term. The impact of the DHPC for olanzapine is characterized by a short-term flattening off of use (increasing slope pre-DHPC and no significant (from null) change in slope post-DHPC), resulting in no significant short-term change in the level of use, but a significant long-term decrease in use post-DHPC (data available upon request).

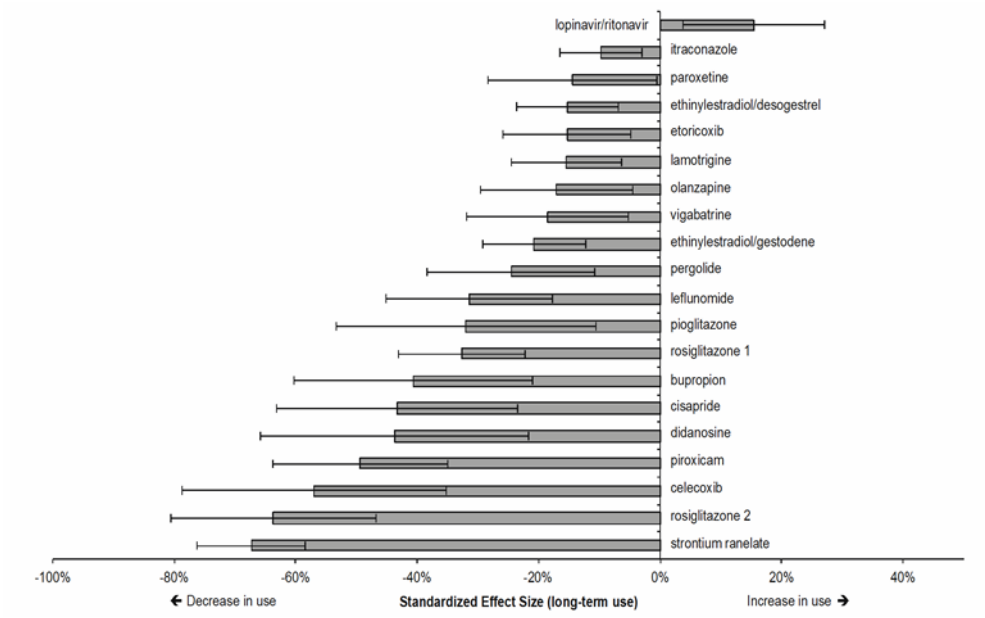

Figure 1. Standardized effect sizes of Direct Healthcare Professional Communications (DHPC) leading to significant long-term changes in volume of new drug use.
Drugs with more than one DHPC are indicated by their number

Discussion

This study is the first to systematically assess the effect of safety-related regulatory action on changes in volume of drug use in ambulatory care over a an extended period. In the short term, almost half of all drugs with a DHPC showed a decrease in use in the year after the DHPC was issued as compared with the year before. Long-term changes in use were observed for a third of the drugs with a DHPC, resulting in a mean decrease of 26.7% in drug use, ranging from −10 to −67%. Changes in use were not clearly related to pre-existent trends in use.

This study shows that DHPCs can lead to a considerable decrease in use of a minority of drugs. The results support earlier reported variation in the effect of safety-related regulatory action. Large reductions in use of coxibs in favour of non-steroidal anti-inflammatory drugs were reported earlier in Germany,[30] and large reductions in use of glitazones have been reported in the United States.[31] Similar to our study, smaller or no decreases in drug use have been reported as well. A decrease of only 20% in overall antipsychotic drug prescriptions to patients with dementia was reported.[32] Use of

isotretinoin did not decrease significantly after a DHPC informing health-care professionals about risk of psychiatric problems.[33]

Several factors might explain the observed decreases in the use of drugs after a DHPC. For example, the observed decreases in use of the coxibs, pergolide, anti-HIV drugs, and bupropion may be explained by the availability of alternative drugs with a more favourable benefit–risk profile (**Table 3**).

Moreover, in the Netherlands, bupropion is also indicated to assist patients in their wish to give up smoking and could therefore be considered a luxury drug, with limited medical need and a low acceptance of drug risks. The severity of the reported adverse drug events, e.g., strontium ranelate (Drug Rash with Eosinophilia Systemic Symptoms (DRESS), the coxibs (cardiovascular risk), glitazones (fracture risk), pergolide (cardiac valve disease), cisapride (QT prolongation), olanzapine (death), and vigabatrin (visual field defects), may explain the significant impact of the related DHPCs on drug use. The second DHPCs for both lamotrigine and paroxetine warned of potential teratogenic effects, which may be considered severe. However, these affect only a distinct subpopulation of women of childbearing age. The observed 15% (lamotrigine) and 16% (paroxetine) decreases in use may thus have been attenuated by evaluating the impact of the DHPCs on overall use, instead of use by this specific group of women alone.

Remarkably, the first DHPC for lopinavir/ritonavir led to increased use, over both the long and the short term. This may be explained by the message of the DHPC, which announced a switch from a capsule to a tablet formulation, which was intended to prevent a safety issue and thus not expected to cause a decrease in prescription rates. Moreover, prescribing of lopinavir/ritonavir is highly valued by many specialists because of the effectiveness of this combination in lowering patients' viral load.[34]

Of note, two-thirds of the DHPCs did not result in long-term changes in drug use. Factors that may explain the absence of long-term changes in our study are a lack of available alternative drugs, as in the case of etanercept, gemfibrozil, hydroxycarbamide, and imatinib (**Table 3**). The high medical need for these drugs in specific populations could overrule concerns prescribers may have with the reported safety issues in the DHPC. A number of DHPCs reported safety issues that were either already known or not unexpected from the underlying mechanism of action; for example, the second DHPCs for celecoxib and cisapride, hormone replacement therapy (breast cancer risk was widely published before the DHPC was issued),[35] sibutramine (potential cardiovascular risk was already known at the time of approval), and pimecrolimus and tacrolimus (immune-modulating agents and risk of lymphomas). In these cases, physicians may have realized the risk associated with these drugs earlier and adapted their prescribing behaviour

Table 3. Potential explanations for (lack of) impact of DHPCs on volume of drug use.

DHPCs with long term changes (decrease in Rx) in use	
Alternative treatment available	bupropion, celecoxib[1], didanosine, etoricoxib, itraconazole, pergolide, stavudine.
Limited medical need	Bupropion.
Severe (new) ADE, including teratogenicity	celecoxib[1], cisapride[1], etoricoxib, itraconazole, lamotrigine[2], leflunomide, olanzapine, paroxetine[2], pergolide, pioglitazone, rosiglitazone[1, 2], strontium ranelate, vigabatrine.
Confirmation of existing doubts/accelerating effect on decreasing drug use at end of its lifecycle	cisapride[1], combinations of desogestrel and gestodene with ethinylestradiol, piroxicam.
DHPC with long term change (increase in Rx) in use	
High medical need	lopinavir/ritanovir[1].
DHPCs without long term changes in use	
No alternative treatment available/high medical need	etanercept, gemfibrozil, hydroxycarbamide, imatinib mesilate.
Known ADE	celecoxib[2], cisapride[2], etanercept, HRT, lamotrigine[1], mycophenolate mofetil, nevirapine, pimecrolimus, rosuvastatin, sibutramine, tacrolimus, tamsulosine.
Rare ADE	tamsulosine, hydroxycarbamide.
Specialist initiates drug therapy	epoetine alfa[1, 2, 3], imatinib mesilate[1, 2], levetiracetam, lopinavir/ritonavir[2], mycophenolate mofetil, nelfinavir[1, 2], pimecrolimus, sirolimus, stavudine, tacrolimus, tenofovir[1, 2, 3, 4], topiramate.
Off label use	botuline a toxin, galantamine hydrobromide, letrozole, salbutamol, triamcinolon acetonide, venlafaxine.
(Preventing) Medication error	levetiracetam, lopinavir/ritanovir[2], nelfinavir[1, 2], repaglinide, somatropin.

Several explanations for (absence of) impact of a DHPC for a drug are possible. Drugs with more than one DHPC are indicated by their superscript numbers.
ADE= Adverse drug event; **DHPC=** Direct Healthcare Professional Communication; **HRT=** Hormone Replacement Therapy; **Rx=** Medical prescription.

accordingly. Some adverse drug events may be rare and considered acceptable risks in the specific populations these drugs are used in, as in the case of tamsulosin (floppy-iris syndrome in the elderly patient) and hydroxycarbamide (cutaneous vasculitis in patients with cancer). Prescription of drugs such as epoetin alfa, imatinib mesilate, and levetiracetam is usually initiated by specialists and subsequently continued in ambulatory care. Specialists make more use of resources such as laboratory tests in comparison to general practitioners, facilitating continued use of drugs with a safety warning.[(36)] DHPCs related to off-label use could be another reason for the absence of a long-term effect. In

such a case, the drug in question is often prescribed only to a small group of patients outside of the regular indication. This could explain the lack of long-term impact of DHPCs for botulin toxin, galantamine, and letrozole. The DHPCs for levetiracetam, lopinavir/ritonavir[2], nelfinavir[1,2], repaglinide, and somatropin were issued to prevent medication errors (including drug–drug interactions). For example, in the DHPC for somatropin, defective calculators were called back that were distributed to prescribers to facilitate dose calculation of the growth hormone.

Half of all included drugs had a decrease in use in the year after the DHPC was issued. For 8 of 13 drugs with a declining use in the year preceding the DHPC, a long-term change in use was observed. This indicates an accelerating effect of the DHPC on already decreasing use of drugs that might be at the end of their life cycle. Although we could not confirm that older drugs more often showed declining use, at the mature stage of a product's life cycle several alternative agents have usually become available. It is likely that the DHPC confirmed already existing doubts of prescribers about the safety of some of these drugs (cisapride, combinations of desogestrel and gestodene with EE, piroxicam), which made them stop prescribing the drugs to new patients. In the cases of cisapride-related cardiac arrhythmias and venous thrombosis related to combinations of desogestrel and gestodene with EE, the safety issues had already been described in the literature,[37,38] whereas the DHPC followed some time afterward.[23] A similar pattern was observed for piroxicam; its use had decreased before the DHPC was issued because of gastrointestinal complications. Nevertheless, we cannot conclude that a pre-existent declining use is an established factor in predicting the effectiveness of a DHPC because we did not observe a statistically significant association.

Further research is needed to determine the impact of the different factors discussed on the effect of DHPCs on use of individual drugs. Such knowledge can help optimize the impact of DHPCs.

Strengths and limitations

Our study expands the limited evidence that currently exists in literature on the impact of DHPCs. Our study includes DHPCs issued over a period of 8 years and a wide range of safety issues representing all main therapeutic classes (ATC) prescribed in ambulatory care. Because the same method was used to assess the impact of DHPCs issued for a wide range of drugs, our results enable the comparison of effects of the different DHPCs. Our study could serve as a starting point for future research aimed at evaluating the impact of safety-related regulatory action.

In our study, we focused on the volume of new drug use as an outcome measure, instead of overall drug use. We assumed new drug use to be more sensitive to changes in

prescribing and therefore more responsive to the impact of safety-related regulatory action. The impact of DHPCs can also be analysed using outcome measures that are directly attuned to the safety issue, for example, occurrence of the adverse event itself[39] or how often health-care professionals perform recommended laboratory tests to identify early potential drug toxicity.[40] These effects remain to be explored further in new studies.

We combined trend regression analysis for short-term evaluation of usage patterns with time series analyses to assess long-term changes in use. Time series analyses account for potential biases in the effect estimate of the intervention, such as secular trends, cyclical effects, random fluctuations, and correlation of adjacent error terms. This affords greater reliability of the measurement than before–after comparisons or linear regression.[41] Although suitable in the short-term, linear regression models cannot appropriately account for possible dependencies among observations over time. The combination of the two strategies allows for a clearer understanding of the impact of a DHPC.

A limitation of our study is that we did not have information on possible concomitant interventions that may have occurred at the same time. However, long-term changes affecting all DHPCs are unlikely given the heterogeneity in the drugs under study and the diverse timing of issuance of the DHPCs. In addition, our study has no control group, because legal requirements specify that DHPCs be sent to all relevant Dutch healthcare professionals. However, interrupted time series analysis is the most appropriate method for studying intervention effects when it is not feasible to define a comparison group.[42] Moreover, we evaluated the impact of DHPCs only in the Netherlands. Healthcare professionals in other countries may respond differently to DHPCs. Similar analyses conducted in other countries would be an interesting route for further research.

Conclusion and recommendation

In conclusion, once safety issues for drugs are identified that warrant strong regulatory action, i.e., DHPCs, these result in substantial long-term reductions in use of only a third of issued DHPCs, independent of pre-existing trends in use. The reason for less impact could be due to factors such as the type of adverse drug event, availability of alternative agents, and the type of prescriber. Further research is needed to determine the influence of these factors, and methods to enhance the impact of DHPCs should be explored.

Acknowledgments

This study was supported by an unconditional grant from the Dutch Medicines Evaluation Board.

References

1 Califf RM. Benefit assessment of therapeutic products: The Centers for Education and Research on Therapeutics. Pharmacoepidemiol Drug Saf 2007 16(1):5-16.

2 Stricker BC, Psaty BM. Detection, verification, and quantification of adverse drug reactions. Br Med J 2004 07;329(7456):44-47.

3 Mol PGM, Straus SMJM, Piening S, De Vries JTN, De Graeff PA, Haaijer-Ruskamp FM. A decade of safety-related regulatory action in the Netherlands: A retrospective analysis of direct healthcare professional communications from 1999 to 2009. Drug Saf 2010 33(6):463-474.

4 Lasser KE, Allen PD, Woolhandler SJ, Himmelstein DU, Wolfe SM, Bor DH. Timing of new black box warnings and withdrawals for prescription medications. J Am Med Assoc 2002 05;287(17):2215-2220.

5 Heemstra HE, Giezen TJ, Mantel-Teeuwisse AK, De Vrueh RLA, Leufkens HGM. Safety-related regulatory actions for orphan drugs in the US and EU: A cohort study. Drug Saf 2010 33(2):127-137.

6 European Medicines Agency. Public statement on Acomplia (rimonabant). Withdrawal of the marketing authorisation in the European Union. 2009; Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2009/11/WC500012189.pdf. Accessed July 15, 2011.

7 European Medicines Agency. European Medicines Agency recommends suspension of Avandia, Avandamet and Avaglim. 2010; Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/public_health_alerts/2010/09/human_pha_detail_000020.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d126. Accessed July 15, 2011.

8 Raine J, Wise L, Blackburn S, Eichler H-, Breckenridge A. European perspective on risk management and drug safety. Clin Pharmacol Ther 2011 89(5):650-654.

9 Leeflang PSH, Wieringa JE. Modelling the effects of pharmaceutical marketing. Mark Lett 2010 21(2):121-133.

10 European Commission. Volume 9A of the rules governing medicinal products in the European Union. Guidelines on Pharmacovigilance for medicinal products for human use. 2008; Available at: http://ec.europa.eu/health/files/eudralex/vol-9/pdf/vol9a_09-2008_en.pdf. Accessed March 24, 2011.

11 Goldman SA. Communication of medical product risk: How effective is effective enough? Drug Saf 2004 2004 27(8):519-534.

12 Woosley RL. Drug labelling revisions - Guaranteed to fail? J Am Med Assoc 2000 12;284(23):3047-3049.

13 Yu DT, Seger DL, Lasser KE, Karson AS, Fiskio JM, Seger AC, et al. Impact of implementing alerts about medication black-box warnings in electronic health records. Pharmacoepidemiol Drug Saf 2011 20(2):192-202.

14 De Vries CS, Van Den Berg PB, De Jong-Van Den Berg LTW. Oral contraceptive use before and after the latest pill scare in the Netherlands: Changes in oral contraceptive use and how users change. Contraception 1998 57(4):247-249.

15 Williams D, Kelly A, Carvalho M, Feely J. Effect of the British warning on contraceptive use in the General Medical Service in Ireland. Ir Med J 1998 91(6):202-203.

16 Smalley W, Shatin D, Wysowski DK, Gurwitz J, Andrade SE, Goodman M, et al. Contraindicated use cisapride: Impact of Food and Drug Administration regulatory action. J Am Med Assoc 2000 12;284(23):3036-3039.
17 Weatherby LB, Walker AM, Fife D, Vervaet P, Klausner MA. Contraindicated medications dispensed with cisapride: Temporal trends in relation to the sending of 'Dear Doctor' letters. Pharmacoepidemiol Drug Saf 2001 10(3):211-218.
18 Wheeler BW, Gunnell D, Metcalfe C, Stephens P, Martin RM. The population impact on incidence of suicide and non-fatal self-harm of regulatory action against the use of selective serotonin reuptake inhibitors in under 18s in the United Kingdom: Ecological study. BMJ 2008 03;336(7643):542-545.
19 Morrato EH, Libby AM, Orton HD, DeGruy III FV, Brent DA, Allen R, et al. Frequency of provider contact after FDA advisory on risk of pediatric suicidality with SSRIs. Am J Psychiatry 2008 165(1):42-50.
20 The European Parliament and The European Council. REGULATION (EU) No 1235/2010. 2010; Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0001:0016:EN:PDF. Accessed January 4, 2010.
21 The European Parliament and The European Council. DIRECTIVE 2010/84/EU. 2010; Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0074:0099:EN:PDF. Accessed January 4, 2011.
22 Foundation for Pharmaceutical Statistics. Facts and figures 2010. 2011; Available at: http://www.sfk.nl/algemeen/2010fandf. Accessed 31 May, 2011.
23 Dutch Medicines Evaluation Board. Direct Healthcare Professional Communications. 2012; Available at: http://www.cbg-meb.nl/CBG/en/human-medicines/pharmacovigilance/DHPC/default.htm. Accessed 10 February, 2012.
24 CBG-MEB. Database Human Medicines. 2011; Available at: http://www.cbg-meb.nl/CBG/en/human-medicines/geneesmiddeleninformatiebank/default.htm. Accessed April 30, 2011.
25 WHO Collaborative Centre for Drug Statistics Methodology. ATC/DDD Index. 2010; Available at: http://www.whocc.no/atc_ddd_index/. Accessed April 30, 2011.
26 Box G, Tiao G. Intervention Analysis with Applications to Economic and Environmental Problems. Journal of the American Statistical Association 1975 70(349):70-79.
27 McDowall D, McCleary R, Meidinger EE, Hay RA. Interrupted Time Series Analysis. Beverly Hills CA: Sage Publications; 1980.
28 Akaike H. New look at the statistical model identification. IEEE Transactions on Automatic Control 1974 AC-19(6):716-723.
29 Schwarz G. Estimating the dimension of a model. The Annals of Statistics 1978 6(2):461-464.
30 Schussel K, Schulz M. Prescribing of COX-2 inhibitors in Germany after safety warnings and market withdrawals. Pharmazie 2006 61(10):878-886.
31 Starner CI, Schafer JA, Heaton AH, Gleason PP. Rosiglitazone and pioglitazone utilization from January 2007 through May 2008 associated with five risk-warning events. J Managed Care Pharm 2008 14(6):523-531.
32 Valiyeva E, Herrmann N, Rochon PA, Gill SS, Anderson GM. Effect of regulatory warnings on antipsychotic prescription rates among elderly patients with dementia: A population-based time-series analysis. CMAJ 2008 08;179(5):438-446.
33 Azoulay L, Oraichi D, Berard A. Patterns and utilization of isotretinoin for acne from 1984 to 2003: Is there need for concern? Eur J Clin Pharmacol 2006 08;62(8):667-674.

34 Croxtall JD, Perry CM. Lopinavir/Ritonavir: a review of its use in the management of HIV-1 infection. Drugs 2010 70(14):1885-1915.
35 Faber A, Bouvy ML, Loskamp L, Van De Berg PB, Egberts TCG, De Jong-Van Den Berg LTW. Dramatic change in prescribing of hormone replacement therapy in the Netherlands after publication of the Million Women Study: A follow-up study. Br J Clin Pharmacol 2005 60(6):641-647.
36 Harrold LR, Field TS, Gurwitz JH. Knowledge, patterns of care, and outcomes of care for generalists and specialists. J Gen Intern Med 1999 14(8):499-511.
37 Wysowski DK, Bacsanyi J. Cisapride and fatal arrhythmia [4]. New Engl J Med 1996 335(4):290-291.
38 Jick H, Jick SS, Gurewich V, Myers MW, Vasilakis C. Risk of idiopathic cardiovascular death and nonfatal venous thromboembolism in women using oral contraceptives with differing progestagen components. Lancet 1995 346(8990):1589-1593.
39 Motola D, Vargiu A, Leone R, Conforti A, Moretti U, Vaccheri A, et al. Influence of regulatory measures on the rate of spontaneous adverse drug reaction reporting in Italy. Drug Saf 2008 31(7):609-616.
40 Willy ME, Manda B, Shatin D, Drinkard CR, Graham DJ. A Study of Compliance with FDA Recommendations for Pemoline (Cylert(registered trademark)). J Am Acad Child Adolesc Psychiatry 2002 41(7):785-790.
41 Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther 2002 27(4):299-309.
42 Eccles M, Grimshaw J, Campbell M, Ramsay C. Research designs for studies evaluating the effectiveness of change an improvement strategies. Qual Saf Health Care 2003 12(1):47-52.

Chapter 4

When Direct Healthcare Professional Communications have an impact on inappropriate and unsafe use of medicines. A retrospective analysis of determinants of impact of safety warnings.

Katrin C. Reber*[1]
Sigrid Piening*[2]
Jaap E. Wieringa[1]
Sabine M. J.M. Straus[3, 4]
June M. Raine[5]
Pieter A. de Graeff[2, 3]
Flora M. Haaijer-Ruskamp[2]
Peter G. M. Mol[2, 3]

* The first two authors contributed equally

Clinical Pharmacology & Therapeutics 2013 93:4 (360-365)

[1] Department of Marketing, University of Groningen, the Netherlands
[2] Department of Clinical Pharmacology, University of Groningen, University Medical Center Groningen, the Netherlands
[3] Dutch Medicines Evaluation Board, Utrecht, the Netherlands
[4] Department of Medical Informatics, Erasmus Medical Center, Rotterdam, the Netherlands
[5] Medicines and Healthcare products Regulatory Agency, London, United Kingdom

Abstract

Serious safety issues relating to drugs are communicated to healthcare professionals via Direct Healthcare Professional Communications (DHPCs). We explored which characteristics determined the impact of DHPCs issued in the Netherlands for ambulatory care drugs (2001-2008).

With multiple linear regression we examined impact on the relative change in new drug use post-DHPC of: time to DHPC, trend in use, degree of innovation, specialist drug, first/repeated DHPC, DHPC template, and type of safety issue.

DHPCs have less impact on use of specialist drugs than non-specialist drugs ($p<0.05$). The DHPCs' impact increased after availability of a template emphasizing the main problem ($p<0.05$), and for safety issues with a risk of death and/or disability (both $p<0.05$) (adjusted $R^2=0.392$).

Risk communication can be effective, specifically in case of well-structured information, and very serious safety issues. Effectiveness may improve by tailoring DHPCs and adding other communication channels, for example for drugs that are increasingly being used.

Introduction

Due to the well-known limitations of pre-approval clinical trials, the safety profile of a drug is only partly known at the time of market entry.[1] Market approval does not signal the end of drug development, but the start of continuous evaluation of both benefits and risks during the entire lifecycle of a drug. Throughout this lifecycle serious safety issues may emerge,[2-4] which can cause hospitalization, disability, or even death of patients.[5,6] Healthcare professionals need to be informed of these safety issues as soon as possible in order to minimize the risk of preventable adverse drug events. In the European Union (EU), these risks are communicated through paper-based warning letters, so-called Direct Healthcare Professional Communications (DHPCs) or 'Dear Doctor Letters'. Over the last decade, risk minimization interventions such as DHPCs have been issued in increasing numbers[2,7] to ensure continued safe and effective use of medicinal products.[8]

However, the limited evidence so-far indicates that DHPCs are not always effective in changing behaviour of physicians.[9,10] Most studies that have assessed the impact of drug safety warnings, focused on one drug or on a limited number of warnings only, and often had methodological limitations.[9] When looking at a large number (58) of different drug safety issues, we showed that DHPCs lowered drug use in half of the cases in the short term, and in a third of the cases in the long term.[11]

With the new EU pharmacovigilance legislation, which came into force in July 2012, evaluation of the impact of risk minimization measures has become mandatory.[12,13] Currently, it is unknown which determinants might influence the impact of DHPCs. A better understanding of the influence of these determinants can facilitate optimization of future risk communication and evaluation of risk minimization measures. In this study we explore the impact of drug and DHPC related characteristics on the effect of DHPCs on drug use.

Methods

Data collection

Data was collected for all drugs for which a DHPC was issued in the Netherlands between January 2001 and January 2008. Monthly dispensing data for the period 2000-2008 were obtained from the Dutch Foundation for Pharmaceutical Statistics (SFK). The SFK database contains drug dispensing data of more than 95% of Dutch community pharmacies, serving approximately 15.3 million people.[14] The DHPCs were collected from the website of the Dutch Medicines Evaluation Board (MEB),[15] and the Dutch Healthcare Inspectorate (IGZ) paper archive. We excluded DHPCs for drugs that were not dispensed in ambulatory care, drugs with insufficient dispensing data (≤ 10 Rx/month for new users, who were not

prescribed the same drug within the previous six months; pre- and post-DHPC), and drugs for which a market withdrawal was announced in the DHPC.

The drug and DHPC characteristics were retrieved from the DHPCs, the human medicines database of the MEB,[16] the World Health Organization ATC classification system, and the Medical Dictionary for Regulatory Activities (MedDRA®, version 13).[1] We recorded the International Non-proprietary Names (INN), Anatomical Therapeutic Chemical (ATC) classification, registration date, date of DHPC, and safety issue (including System Organ Class).

Data measurement

Outcome measure

The outcome measure for this study was the relative change in new drug use after a DHPC was issued. We defined new drug use as the number of new prescriptions of a drug for which no prescriptions were dispensed to the patient in the previous six months. We chose new drug use as our outcome measure since we assumed it to be more sensitive to changes in prescribing than overall drug use. The relative change was calculated as the absolute change in drug use divided by the median drug use in the 12 months before the DHPC. Changes in the absolute number of new drug use were determined through interrupted time series analyses based on separate autoregressive integrated moving average (ARIMA) models for each individual drug. Observed changes indicated a change in the level of new use from the time of the DHPC until the end of the observation period. The calculation of the outcome measure and in- and exclusion criteria were described in more detail elsewhere.[11]

Determinants

Characteristics of the drugs and the DHPC were assessed to explain differences in the outcome. We included four drug related characteristics: (1) The **time to DHPC,** defined as the elapsed time in months from drug approval (registration date) to the publication of the DHPC. (2) **Trends in use before the DHPC,** based on trend analyses[11] to identify changes in the number of new users in the 12 months before the publication of the DHPC. (3) The **degree of therapeutic innovation** was determined by using the score of

[1] The MedDRA terminology is the international medical terminology developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. MedDRA is a registered trademark of the International Federation of Pharmaceutical Manufacturers and Associations.

therapeutic innovation as reported by Motola et al. for drugs that were centrally approved in Europe.[17] Using this score, drugs can be classified as important, moderate, modest, or as solely pharmacological/technological innovations, taking into account the seriousness of the disease, the availability of alternative drugs and whether drug effects have been shown on relevant clinical endpoints and observed effect size. For the drugs that were approved via the decentralized system, that is at the national level, two investigators (PM and PdG) independently evaluated the degree of therapeutic innovation using the 'Motola algorithm'. In case of disagreement consensus was reached by discussion. (4) **Specialist drugs**, i.e. the drug required an initial prescription from a medical specialist as indicated in the Summary of Product Characteristics (SmPC).

The following three DHPC related characteristics were included: (1) **First or repeated DHPC,** a dichotomous variable indicating whether the DHPC was the first safety-related regulatory action or whether another DHPC had been sent previously. This included identical as well as different safety issues. (2) **DHPC template,** a dichotomous variable indicating whether the DHPC was issued after a DHPC template was published in Volume 9A of 'The rules governing medicinal products in the European Union' in January 2007. (3) The **type of serious safety issue**, which was classified according to the World Health Organisation listing of serious adverse events or reactions, as resulting into: death, (prolongation of) hospitalization, and persistent or significant disability/incapacity.[18] We added a category 'other' for cases that could not be classified into any of the aforementioned categories, e.g. product contamination. Two pharmacovigilance experts (medical doctors) independently categorized the adverse drug reactions. Any disagreement was resolved by a third expert (PM).

Statistical Analyses

We performed a multiple linear regression analysis to examine the impact of drug and DHPC characteristics on the observed relative change in new drug use following a DHPC. As the assumption of homoscedasticity, one of the key assumptions in linear regression,[19] was not fulfilled, a weighted least squares procedure was applied. The size of the weight was inversely related to the uncertainty of the information contained in the associated data point. The point estimates of relative changes in new drug use weighed less when the observed absolute changes in effect sizes were found to have higher standard errors in the ARIMA model. The independent variables were entered block wise, with the variables describing the drug characteristics entering in the first block. The second block included the DHPC characteristics. The degree of therapeutic innovation was treated as a continuous, independent variable in the analysis. The explained variance of the model was indicated by the adjusted R^2. The significance of each block was tested using F change, and

the contribution of each block to the variance explained was computed (Δ R^2). Raw coefficients (B) with 95% confidence intervals (CIs), standardized beta coefficients (β), and P values were calculated. Statistical analyses were performed with SPSS 18 (SPSS Inc., Chicago, Illinois).

Results

We identified 59 DHPCs for 46 drugs that fulfilled all in- and exclusion criteria. Two DHPCs that were issued within two consecutive months for nelfinavir were analysed as one. This resulted in 58 evaluable drug & DHPC pairs for which the relative changes in new drug use following the DHPC were calculated (**Table 1**). The median number of new drug users per month in the year before the DHPC ranged from 7 (sirolimus) to 53,596 (salbutamol) (**Appendix table**).

The mean relative change in new drug use among all DHPCs analysed was -9% (SD: ±2.4%) and ranged from -67.4% for strontium ranelate to +71.7% for sirolimus (**Appendix table**). The median time from approval to DHPC was 82.5 months (6.9 years, IQR: 3.4 – 13.6) and 80% of the DHPCs were issued for drugs that had been licensed for more than three years. Almost a quarter of the drugs showed a decrease in new drug use prior to the DHPC. Similar numbers of DHPCs were issued for all drugs independent of their degree of innovation (important, moderate and solely pharmacological/technological) with a few drugs classified as modestly innovative. More than half (59%) of the DHPCs were sent for specialist drugs. The majority (71%) of the 58 DHPCs concerned a first DHPC. DHPCs were evenly divided over the seriousness categories.

When the first block with the drug characteristics was entered in the model to test if these characteristics explained any differences in the impact of the DHPC on drug use, we found that DHPCs sent for specialist drugs were associated with a more positive change in use than the change in use of non-specialist drugs (**Table 2**; Model 1, p=0.046). Within the group of drugs for which the DHPC leads to a decrease in use, the positive β value indicated that the negative usage effect was (partially) offset for specialist drugs. Conversely, for the cases where a DHPC increased drug use, the increase was stronger for specialist drugs than for non-specialist drugs. This effect remained significant after entering the DHPC characteristics in the model (**Table 2**; Model 2, p=0.008). In the second model, we also found that DHPCs for drugs with a decreasing pre-DHPC trend were associated with a change towards lower drug use; this effect was marginally significant (**Table 2**; Model 2, p=0.055). DHPCs issued after a template was made available contributed to a change towards lower drug use (**Table 2**; Model 2, p<0.05). Both safety issues with a risk of death and disability were significantly associated with changes issues with a risk of death and disability were significantly associated with changes towards

Table 1. Descriptive statistics for outcome and independent variables

Variable	Drug & DHPC pair[a]
Sample	58
Outcome measure (Relative change in new drug use)	
Mean (SD)	-0.09 (0.24)
Range	-0.674 to 0.717
Independent variables	
Drug characteristics:	
Time to DHPC since registration	
Median, year (IQR)	6.9 (3.4 - 13.6)
≤ 3, year (%)	12 (20.7)
>3-10, year (%)	23 (39.7)
>10, year (%)	23 (39.7)
Trends in use (before DHPC was issued), No. (%)	
increasing use	16 (27.6)
no change in use	29 (50,0)
decreasing use	13 (22.4)
Degree of therapeutic innovation, No. (%)	
important	23 (39.7)
moderate	12 (20.7)
modest	4 (6.9)
mere pharmacological/ technological	19 (32.8)
Specialist drug, No. (%)	
no	24 (41.4)
yes	34 (58.6)
DHPC characteristics:	
First/repeated DHPC, No. (%)	
first	41 (70.7)
repeated	17 (29.3)
DHPC template, No. (%)	
no	47 (81.0)
yes	11 (19.0)
Type of serious safety issue, No. (%)	
death	10 (17.2)
(prolonged) hospital admission	17 (29.3)
(temporary/persistent) disability or incapacity/teratogenicity	18 (31.0)
other	13 (22.4)

a Unless otherwise indicated, data are reported as numbers (percentages) of drug & DHPC pairs. Percentages might not add up to 100% due to rounding.
SD= standard deviation, **IQR**=interquartile range, **y**=years

lower drug use (**Table 2**; Model 2, p<0.05 for both), whereas no significant impact was observed for safety issues regarding the risk of hospitalization (**Table 2**; Model 2, p=0.867).

The block of DHPC characteristics contributed significantly to the model, explaining an additional 32% of variance (F-change=5.906, ΔR^2=0.315, p≤0.001). The drug and DHPC

Table 2. Results of the weighted regression analysis[a]

	Blocks entered in the analysis	Model 1 (block 1 entered)			Model 2 (both blocks entered)		
		B [95% CI]	β	P value	B [95% CI]	β	P value
	(constant)	-0.214 [-0.386; -0.042]		0.016	-0.043 [-0.212; 0.126]		0.608
Block 1: drug	**Time to DHPC (months)**	$3.05*10^{-4}$ [-0.000; 0.001]	0.149	0.257	$1.67*10^{-4}$ [-0.000; 0.001]	0.082	0.478
	Trend in use (before DHPC)						
	increasing	ref	ref		ref	ref	
	no change	0.036 [-0.097; 0.169]	0.084	0.593	0.011 [-0.106; 0.128]	0.025	0.854
	decreasing	-0.080 [-0.242; 0.082]	-0.160	0.324	-0.135 [-0.273; -0.003]	-0.270	0.055
	Degree of therapeutic innovation [b]	-0.002 [-0.057; 0.052]	-0.013	0.934	0.004 [-0.044; 0.053]	0.025	0.860
	Specialist drug						
	No	ref	ref		ref	ref	
	Yes	0.136 [0.002; 0.269]	0.320	**0.046**	0.159 [0.043; 0.274]	0.373	**0.008**
Block 2: DHPC	**First/repeated DHPC**						
	First				ref	ref	
	Repeated				-0.092 [-0.213; 0.029]	-0.187	0.133
	DHPC template						
	No				ref	ref	
	Yes				-0.157 [-0.266; -0.049]	-0.308	**0.005**
	Type of serious safety issue						
	Death				-0.265 [-0.415; -0.114]	-0.450	**0.001**
	Hospital admission				-0.012 [-0.152; 0.129]	-0.025	0.867
	Disability/Incapacity/Teratogenicity				-0.155 [-0.288; -0.023]	-0.348	**0.023**
	Other				ref	ref	
	R^2 (adjusted R^2)		0.184 (0.106)			0.499 (0.392)	
	ΔR^2					0.315	
	F change					5.906	0.000

a A negative regression coefficient is associated with a lower use post DHPC (i.e., a larger decrease or a smaller increase as a result of the DHPC). **b** Treated as continuous predictor.**B=** raw regression coefficient; **95% CI=** 95% confidence interval; **β=** standardized regression coefficient; **ref=** reference category.

characteristics together explained 39% (adj. R^2=0.392) of the overall variation in change of new drug use.

Discussion

This study gives a first impression of the determinants that increase the impact of DHPCs on drug use. We found that declining drug use prior to the DHPC, specialist drugs, the type of serious safety issue, and DHPCs that were issued after the DHPC template was made available were associated with changes in drug use. We discuss the comments from the viewpoint of the most common situation that a DHPC leads to a decrease in the number of new users.

The marginally significant effect found for already declining use pre DHPC confirms our earlier assumption that DHPCs have an accelerating effect on the decline in use of drugs that are at the end of their lifecycle, when several substitute drugs have become available.[11]

As hypothesized earlier,[11] we observed that DHPCs issued for drugs that require a specialist to initiate prescribing have less impact compared to those sent for drugs that can also be prescribed by a GP. Drugs are given this requirement in the SmPC, because of the expected complexity in prescribing them. The specialist drugs in our sample were mainly prescribed for the human immunodeficiency virus (HIV), epilepsy and cancer. Specialists often have additional resources at their disposal to monitor their patients, which facilitates continued use of a drug post DHPC.[20] Also, specialists might tend to use more risky treatment options in view of the patient population they treat (e.g. more complex patients, patients that previously failed on other therapies). Another explanation could be that the perception of their own expertise limits their willingness to accept recommendations from others, as was observed during implementation of treatment guidelines.[21] Towards the end of our study period the European guidelines were amended to include a fixed DHPC template.[8] When we analysed the content of the DHPCs in our sample, we observed an increase in uniformity of the structure and layout of the DHPCs. The results of our analysis confirm that DHPCs that were issued after the DHPC template was made available had more impact compared to DHPCs issued before the availability of the template, suggesting that the DHPC template has contributed to the understandability and uptake of the safety information, which would be in line with earlier findings that explicit wording contributes to improved uptake of DHPC recommendations.[22] The increased impact of more recent DHPCs also reflects a generally increased risk awareness due to intensified media accessibility and rapid information availability.[23] Extensive media attention for certain drug safety issues (e.g. rofecoxib,

rosiglitazone) and more proactive pharmacovigilance in the last decade may have further contributed to the awareness of prescribers regarding drug safety warnings.[24]

Communicating on serious safety issues potentially causing death or disability led to significantly lower drug use. Even though all DHPCs are issued for serious safety issues, it is to be expected that these particularly serious safety issues will affect the prescribing behaviour of physicians more.[11]

The impact of DHPCs is not influenced by the age of the drug, indicating that DHPCs affect the use of older and younger drugs in the same way. This is consistent with our earlier finding that important safety issues requiring DHPCs are identified throughout the entire lifecycle of drugs,[2] which would indicate that the age of the drug does not need to be considered when tailoring the communicating drug safety issues.

More innovative drugs did not show greater impact of a DHPC on drug use than less innovative drugs. Therapeutically innovative drugs can provide physicians with treatment options for complex patients who do not respond well to less innovative drugs. Physicians could be of the opinion that the innovativeness of the drug outweighs the risk of occurrence of the safety issue. However, our level of analysis does not allow us to elaborate how this translates to behaviour of individual physicians. This aspect could be explored in a focus group setting or by conducting individual interviews with prescribers.

Our results show that a repeated safety warning is not necessarily more effective in changing drug use than a single DHPC. This is consistent with findings of several prior studies that reported no changes in the assessed outcome after repeated safety warnings were issued.[25-28] The repeated DHPCs in our sample concerned both identical as well as different safety issues. Possibly, repeated DHPCs that were issued for the same safety issue are more effective than repeated DHPCs that were issued for different safety issues with the same drug. However, due to the limited sample size, we were not able to incorporate this aspect into our model.

Strengths and limitations

To our knowledge, this study is the first to systematically evaluate determinants of the impact of DHPCs on new drug use. We included a large number of DHPCs in our analyses, covering a wide variety of drugs and safety issues. With the results of this study it will be possible to anticipate and possibly enhance the impact of future DHPCs on drug use, by tailoring risk communication about safety issues of drugs more specifically. On a case by case basis it can be decided to add other communication channels in addition to the DHPC to obtain the desired outcome: minimisation of the risk. Communication tools additional to the DHPC should be considered for specialist drugs, in case of safety issues leading to hospitalization, and for drugs of which the use is on the rise or at a stable plateau before

the DHPC is issued. For example, an additional e-mail could prove to be a useful and easy tool to rapidly inform healthcare professionals of safety issues. Professional associations and specialist learned societies should be involved in drafting DHPCs for specialist drugs, for a more motivating outreach to reduce prescribing if that is the desired outcome. Repetition of the message for example by professional associations to their members, either by e-mail or in their news bulletins could also improve the impact of the communication. While in case of the most severe safety issues that can lead to disability and/or death of the patient, one clear and strong DHPC might be sufficient. To make the DHPC stand out more to healthcare professionals, they should all be sent with an extra symbol such as a picture of an orange hand printed on the envelope, as is currently done in the Netherlands in cases that require immediate action from the healthcare professional. A different colour, .e.g. yellow could be used to distinguish DHPCs to merely alert healthcare professionals of a drug safety issue from cases where immediate action is required.

We included a set of seven factors in our full model, however, the range of determinants is limited due to the sample size and its corresponding power. Our full model explained 39% of the overall variation in DHPC effect size and can be considered as a first exploration of determinants that influence the impact of DHPCs. Other factors, which we did not include in our model might also attribute to variations in the impact of DHPCs, for example media attention, the incidence of safety issues, safety issues related to off-label use, and availability of an alternative treatment. It is suggested that media attention can play an important role in the impact of DHPCs.[29] To probe this, we performed an explorative lay- and professional literature search for a selection of the DHPCs in our study population. This search resulted in too little information to include presence of media attention in our model. Likewise, the incidence of the safety issue could not be included, since this aspect was not mentioned in the majority of the DHPCs. Too few DHPCs concerned safety issues related to off label use, which led to insufficient variation within the variable for incorporation into our model. Alternative treatment was available for almost all drugs and was indirectly covered in the innovation variable. We did not find associations for older versus newer drugs and degree of innovation with DHPC impact. Therefore, it seems unlikely that availability of an alternative treatment is a major determinant. The limited sample size could be addressed by repeating this study in a few years, when more DHPCs will be issued.

In addition, our study was limited to the Dutch setting, and extrapolation of these findings to hospital drugs is not possible. An EU wide study would allow for a comparison of the impact of DHPCs as well as the determinants of impact of DHPCs in different countries.

This will provide much needed information regarding locally tailored risk communicating strategies.

It should be noted that a decrease in use is not always the desired impact of a DHPC. The results of this study can thus only be used to anticipate the impact of DHPCs on new drug use, not for other outcomes that might be more attuned to the recommendation in the DHPC, such as necessity for liver function tests performed in case of risk of hepatotoxicity. This means that any additional action should be carefully considered. Nevertheless, we think that new drug use is the most appropriate outcome measure to explore the role of determinants of impact of DHPCs, since it is the single outcome measure that can reliably be assessed for such a large group of drugs. Also, new use is a more sensitive measure than overall use, since changes in prescribing behaviour can more likely be expected in new users. Further research could be aimed at clusters of drugs with the same recommendation in the DHPC, e.g. all drugs which require laboratory testing, or all drugs with restrictions regarding concomitant use of contraindicated drugs. This may provide insight into how the impact of DHPCs on more specific outcomes can best be anticipated.

Conclusion and recommendation

This study provides a first exploration of determinants that influence the impact of DHPCs on drug use. The results show that declining use prior to the DHPC, specialist drugs, DHPCs issued after availability of a template, and the type of serious safety issue are associated with changes in new drug use. These results can be used as a first step in tailoring risk communication about safety issues of drugs more specifically.

Acknowledgements

This study was supported by an unconditional grant of the Dutch Medicines Evaluation Board.

References

1 Stricker BC, Psaty BM. Detection, verification, and quantification of adverse drug reactions. Br Med J 2004 07;329(7456):44-47.

2 Mol PGM, Straus SMJM, Piening S, De Vries JTN, De Graeff PA, Haaijer-Ruskamp FM. A decade of safety-related regulatory action in the Netherlands: A retrospective analysis of direct healthcare professional communications from 1999 to 2009. Drug Saf 2010 33(6):463-474.

3 Giezen TJ, Mantel-Teeuwisse AK, Straus SMJM, Schellekens H, Leufkens HGM, Egberts ACG. Safety-related regulatory actions for biologicals approved in the United States and the European Union. J Am Med Assoc 2008 10;300(16):1887-1896.

4 Lasser KE, Allen PD, Woolhandler SJ, Himmelstein DU, Wolfe SM, Bor DH. Timing of new black box warnings and withdrawals for prescription medications. J Am Med Assoc 2002 05;287(17):2215-2220.

5 Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: Prospective analysis of 18 820 patients. Br Med J 2004 07;329(7456):15-19.

6 Sari AB-, Sheldon TA, Cracknell A, Turnbull A, Dobson Y, Grant C, et al. Extent, nature and consequences of adverse events: Results of a retrospective casenote review in a large NHS hospital. Qual Saf Health Care 2007 16(6):434-439.

7 Nkeng L, Cloutier A-, Craig C, Lelorier J, Moride Y. Impact of regulatory guidances and drug regulation on risk minimization interventions in drug safety: A systematic review. Drug Saf 2012 35(7):535-546.

8 European Commission. Volume 9A of the rules governing medicinal products in the European Union. Guidelines on Pharmacovigilance for medicinal products for human use. 2008; Available at: http://ec.europa.eu/health/files/eudralex/vol-9/pdf/vol9a_09-2008_en.pdf. Accessed March 24, 2011.

9 Piening S, Haaijer-Ruskamp FM, De Vries JTN, Van Der Elst ME, De Graeff PA, Straus SMJM, et al. Impact of safety-related regulatory action on clinical practice: A systematic review. Drug Saf 2012 35(5):373-385.

10 Dusetzina SB, Higashi AS, Dorsey ER, Conti R, Huskamp HA, Zhu S, et al. Impact of FDA drug risk communications on health care utilization and health behaviors: A systematic review. Med Care 2012 50(6):466-478.

11 Piening S, Reber KC, Wieringa JE, Straus SMJM, de Graeff PA, Haaijer-Ruskamp FM, et al. Impact of Safety-Related Regulatory Action on Drug Use in Ambulatory Care in the Netherlands. Clin Pharmacol Ther 2012 04;91(5):838-845.

12 The European Parliament and The European Council. REGULATION (EU) No 1235/2010. 2010; Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0001:0016:EN:PDF. Accessed January 4, 2010.

13 he European Parliament and The European Council. DIRECTIVE 2010/84/EU. 2010; Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0074:0099:EN:PDF. Accessed January 4, 2011.

14 Foundation for Pharmaceutical Statistics. Available at: http://www.sfk.nl/english. Accessed 16 October, 2012.

15 Dutch Medicines Evaluation Board. Direct Healthcare Professional Communications. 2012; Available at: http://www.cbg-meb.nl/CBG/en/human-medicines/pharmacovigilance/DHPC/default.htm. Accessed 10 February, 2012.
16 CBG-MEB. Database Human Medicines. 2011; Available at: http://www.cbg-meb.nl/CBG/en/human-medicines/geneesmiddeleninformatiebank/default.htm. Accessed April 30, 2011.
17 Motola D, De Poeti F, Rossi P, Martini N, Montanaro N. Therapeutic innovation in the European Union: Analysis of the drugs approved by the EMEA between 1995 and 2003. Br J Clin Pharmacol 2005 59(4):475-478.
18 World Health Organisation Collaborating Centre for International Drug Monitoring. Glossary of terms in Pharmacovigilance. 2011; Available at: http://www.who-umc.org/graphics/25301.pdf. Accessed December 9, 2011.
19 Greene WH. Econometric Analysis. 6th ed. Upper Saddle River, New Jersey: Prentice Hall; 2008.
20 Harrold LR, Field TS, Gurwitz JH. Knowledge, patterns of care, and outcomes of care for generalists and specialists. J Gen Intern Med 1999 14(8):499-511.
21 Kasje WN, Denig P, Haaijer-Ruskamp FM. Specialists' expectations regarding joint treatment guidelines for primary and secondary care. Int J Qual Health Care 2002 14(6):509-518.
22 Weatherby LB, Nordstrom BL, Fife D, Walker AM. The impact of wording in "Dear doctor" letters and in black box labels. Clin Pharmacol Ther 2002 12;72(6):735-742.
23 Ropeik D, Slovic P. Risk communication: a neglected tool in protecting public health. Risk in Perspective 2003 11(2).
24 Raine J, Wise L, Blackburn S, Eichler H-, Breckenridge A. European perspective on risk management and drug safety. Clin Pharmacol Ther 2011 89(5):650-654.
25 Kurdyak PA, Juurlink DN, Mamdani MM. The effect of antidepressant warnings on prescribing trends in Ontario, Canada. Am J Public Health 2007 97(4):750-754.
26 Kurian BT, Ray WA, Arbogast PG, Fuchs DC, Dudley JA, Cooper WO. Effect of regulatory warnings on antidepressant prescribing for children and adolescents. Arch Pediatr Adolesc Med 2007 161(7):690-696.
27 Olfson M, Marcus SC, Druss BG. Effects of food and drug administration warnings on antidepressant use in a national sample. Arch Gen Psychiatry 2008 65(1):94-101.
28 Jones JK, Fife D, Curkendall S, Goehring Jr. E, Guo JJ, Shannon M. Coprescribing and codispensing of cisapride and contraindicated drugs. J Am Med Assoc 2001 10;286(13):1607-1609.
29 Martin RM, May M, Gunnell D. Did intense adverse media publicity impact on prescribing of paroxetine and the notification of suspected adverse drug reactions? Analysis of routine databases, 2001-2004. Br J Clin Pharmacol 2006 61(2):224-228.

Appendix table 1. Characteristics of DHPCs with and without long term impact on drug use.

DHPCs with significant long-term changes in use											
Drug Characteristics				**DHPC Characteristics**				**Drug use**		**DHPC impact**	
INN (ATC)	**Appr. date**	**Initial pre-scriber**	**Inno-vative-ness**	**DHPC date**	**First/Re-peated DHPC**	**Safety issue (SOC)**	**Type of serious safety issue**	**Median Rx before**	**Trend**	**Change in new drug use**	
										Absolute (SE)	**Relative**
cisapride[1] (A03FA02)	Jul-88	S	4	Sep-02	repeat	Electrocardiogram QT prolonged (Investigations)	F	4148.5	↓	-1797.29 (420.10)	-0.433
rosiglitazone[1] (A10BG02)	Jul-00	GP	1	Jan-06	first	Macular oedema (Eye)	D	1488	0	-486.49 (79.35)	-0.327
rosiglitazone[2] (A10BG02)	Jul-00	GP	1	Mar-07	repeat	Fracture (Musculoskeletal)	D	964	↓	-614.12 (83.39)	-0.637
pioglitazone (A10BG03)	Oct-00	GP	1	Apr-07	first	Fracture (Musculoskeletal)	D	1012	0	-323.43 (110.85)	-0.320
desogestrel / ethinylestradiol (G03AA09)	May-81	GP	1	Sep-01	first	Venous thrombosis (Vascular)	H	10605	↓	-1618.97 (455.50)	-0.153
gestodene / ethinylestradiol (G03AA10)	May-89	GP	1	Sep-01	first	Venous thrombosis (Vascular)	H	5719.5	↓	-1187.13 (247.83)	-0.208
itraconazole (J02AC02)	Oct-90	GP	3	May-01	first	Cardiac failure (Cardiac)	O	8834.5	↓	-860.33 (305.63)	-0.097
lopinavir / ritonavir[1] (J05AE06)	Mar-01	S	4	Sep-06	first	Circumstance or information capable of leading to medication error (Injury)	O	94.5	0	14.55 (5.62)	0.154
didanosine (J05AF02)	Aug-00	S	4	Mar-05	repeat	Drug effect decreased (General)	H	40.5	↓	-17.72 (4.56)	-0.438
leflunomide (L04AA13)	Sep-99	S	1	Mar-01	first	Hepatitis (Hepatobiliary)	F	432	↓	-135.92 (30.38)	-0.315
piroxicam (M01AC01)	Jun-87	GP	1	Aug-07	first	Gastrointestinal disorder (Gastrointestinal)	D	2920.5	↓	-1442.00 (214.23)	-0.494

Appendix table 1. Continued

DHPCs with significant long-term changes in use											
Drug Characteristics				**DHPC Characteristics**				**Drug use**		**DHPC impact**	
INN (ATC)	**Appr. date**	**Initial pre-scriber**	**Inno-vati-ve-ness**	**DHPC date**	**First/Re-peated DHPC**	**Safety issue (SOC)**	**Serious-ness**	**Median Rx before**	**Trend**	**Change in new drug use**	
										Absolute (SE)	**Relative**
celecoxib[1] (M01AH01)	May-00	GP	1	Dec-04	first	Cardiovascular disorder (Cardiac)	F	11851.5	↑	-6751.75 (1314.84)	-0.570
etoricoxib (M01AH05)	Jul-02	GP	1	Feb-05	first	Cardiovascular disorder (Cardiac)	H	12375.5	0	-1898.57 (666.33)	-0.153
strontium ranelate (M05BX03)	Sep-04	GP	3	Nov-07	first	Drug rash with eosinophilia and systemic symptoms: DRESS (Blood)	F	344.5	↑	-232.04 (15.6)	-0.674
vigabatrin (N03AG04)	Sep-90	S	3	Sep-02	repeat	Visual field defect (Nervous)	D	40	0	-7.43 (2.72)	-0.186
lamotrigine[2] (N03AX09)	Jan-96	S	3	Jun-06	repeat	Maternal drugs affecting foetus (Injury)	D	746	0	-115.28 (34.67)	-0.155
pergolide (N04BC02)	Jul-91	S	3	Apr-05	first	Cardiac valve disease (Cardiac)	D	142	0	-34.85 (10.04)	-0.245
olanzapine (N05AH03)	Sep-96	GP	3	Mar-04	first	Death (General)	F	2193	↑	-374.05 (140.18)	-0.171
paroxetine[2] (N06AB05)	Jun-91	GP	2	Mar-06	repeat	Maternal drugs affecting foetus (Injury)	D	10613	↑	-1534.58 (752.14)	-0.145
bupropion (N06AX12)	Dec-99	GP	3	May-01	first	Convulsion (Nervous)	D	4399.5	0	-1785.26 (440.44)	-0.406
DHPCs without significant long-term changes in use											
cisapride[2] (A03FA02)	Jul-88	S	4	Sep-04	repeat	Electrocardiogram QT prolonged (Investigations)	O	408.5	↓	63.49 (419.54)	0.155
sibutramine (A08AA10)	Apr-01	GP	1	Jul-02	first	Cardiovascular disorder (Cardiac)	O	567.5	0	0.29 (100.02)	0.001
repaglinide (A10BX02)	Aug-98	GP	1	May-03	first	Hypoglycaemia (Endocrine)	H	47.5	0	-9.18 (8.51)	-0.193

Appendix table 1. Continued

DHPCs without significant long-term changes in use											
Drug Characteristics				**DHPC Characteristics**				**Drug use**		**DHPC impact**	
INN (ATC)	**Appr. date**	**Initial pre-scriber**	**Inno-vati-ve-ness**	**DHPC date**	**First/Re-peated DHPC**	**Safety issue (SOC)**	**Type of serious safety issue**	**Median Rx before**	**Trend**	**Change in new drug use**	
										Absolute (SE)	**Relative**
epoetine alfa[1] (B03XA01)	Nov-88	S	4	Nov-01	first	Aplasia pure red cell (Blood)	H	417	↑	32.42 (55.88)	0.078
epoetine alfa[2] (B03XA01)	Nov-88	S	4	Jul-02	repeat	Aplasia pure red cell (Blood)	H	495.5	↑	99.64 (55.66)	0.201
epoetine alfa[3] (B03XA01)	Nov-88	S	4	Dec-02	repeat	Aplasia pure red cell (Blood)	H	551.5	↑	-62.85 (55.05)	-0.114
rosuvastatin (C10AA07)	Nov-02	GP	1	Jun-04	first	Rhabdomyolysis (Musculoskeletal)	H	5968.5	0	726.26 (711.06)	0.122
gemfibrozil (C10AB04)	Jul-90	GP	3	May-03	first	Hypoglycaemia (Endocrine)	H	595	↓	17.30 (53.41)	0.029
tacrolimus (D11AX14)	Apr-96	S	4	Apr-06	first	Lymphoma (Blood)	D	1550.5	0	-308.22 (210.02)	-0.199
pimecrolimus (D11AX15)	Apr-03	S	1	Apr-06	first	Lymphoma (Blood)	D	913.5	↓	-67.97 (103.45)	-0.074
hormone suppletion therapy (G03F)	Jul-76	GP	4	Dec-03	first	Breast cancer (Neoplasms)	H	2951	↓	307.82 (345.68)	0.104
tamsulosin (G04CA02)	Apr-95	GP	1	Aug-06	first	Floppy iris syndrome (Nervous)	D	6142	0	100.36 (313.28)	0.016
somatropin (H01AC01)	Nov-91	S	1	Jun-07	first	Circumstance or information capable of leading to medication error (Injury)	O	116.5	0	-16.81 (12.47)	-0.144
triamcinolone acetonide (H02AB08)	Sep-66	GP	2	Dec-06	first	Eye disorder (Eye)	O	11643.5	0	-1055.56 (863.04)	-0.091
nelfinavir[1, 2] (J05AE04)	Jan-98	S	4	Jun-07 & Jul-07*	first	Therapeutic product contamination (Injury)	O	15.5	0	-2.09 (3.58)	-0.139

Appendix table 1. Continued

DHPCs without significant long-term changes in use											
Drug Characteristics				**DHPC Characteristics**				**Drug use**		**DHPC impact**	
INN (ATC)	**Appr. date**	**Initial pre-scriber**	**Inno-vati-ve-ness**	**DHPC date**	**First/Re-peated DHPC**	**Safety issue (SOC)**	**Type of serious safety issue**	**Median Rx before**	**Trend**	**Change in new drug use**	
										Absolute (SE)	**Relative**
lopinavir / ritonavir[2] (J05AE06)	Mar-01	S	4	Aug-07	repeat	Incorrect dose administered (Injury)	H	109.5	0	3.90 (5.44)	0.036
stavudine (J05AF04)	May-96	S	4	Sep-01	first	Muscular weakness (Nervous)	F	73.5	0	-3.29 (5.94)	-0.045
tenofovir[1] (J05AF07)	Feb-02	S	4	Jul-03	first	Drug effect decreased (General)	O	97.5	↓	20.09 (20.21)	0.206
tenofovir[2] (J05AF07)	Feb-02	S	4	Oct-03	repeat	Drug effect decreased (General)	O	97.5	↑	-27.70 (20.23)	-0.284
tenofovir[3] (J05AF07)	Feb-02	S	4	Mar-05	repeat	Drug effect decreased (General)	H	137	0	-1.36 (20.21)	-0.010
tenofovir[4] (J05AF07)	Feb-02	S	4	Mar-06	repeat	Renal disorder (Renal)	D	167.5	↑	27.33 (20.30)	0.163
nevirapine (J05AG01)	Feb-98	S	4	Feb-04	repeat	Skin reaction (Skin)	F	86.5	0	3.03 (7.30)	0.035
imatinib mesilate[1] (L01XE01)	Nov-01	S	4	Mar-05	first	Urinary bladder adenoma (Renal)	O	37.5	↑	7.06 (7.02)	0.188
imatinib mesilate[2] (L01XE01)	Nov-01	S	4	Dec-06	repeat	Cardiac failure (Cardiac)	H	53.5	0	-10.53 (7.66)	-0.197
hydroxycarbamide (L01XX05)	Nov-72	S	3	Dec-05	first	Cutaneous vasculitis (Skin)	D	133	0	6.19 (4.93)	0.047
letrozole (L02BG04)	Jan-97	S	1	Dec-05	first	Maternal drugs affecting foetus (Injury)	D	240.5	↑	33.33 (19.43)	0.139
mycophenolate mofetil (L04AA06)	Feb-96	S	4	Nov-07	first	Maternal drugs affecting foetus (Injury)	D	274	0	-7.78 (14.88)	-0.028
sirolimus (L04AA10)	Mar-01	S	1	Feb-03	first	Bronchial anastomosis complication (Respiratory)	F	6.5	0	4.66 (2.67)	0.717
etanercept (L04AB01)	Feb-00	S	4	Feb-03	repeat	Infection (Infections)	H	28	↑	-1.14 (23.31)	-0.041

Appendix table 1. Continued

DHPCs without significant long-term changes in use											
Drug Characteristics				**DHPC Characteristics**				**Drug use**		**DHPC impact**	
INN (ATC)	**Appr. date**	**Initial pre-scriber**	**Inno-vati-ve-ness**	**DHPC date**	**First/ Repeat-ed DHPC**	**Safety issue (SOC)**	**Type of serious safety issue**	**Median Rx before**	**Trend**	**Change in new drug use**	
										Absolute (SE)	**Relative**
celecoxib[2] (M01AH01)	May-00	GP	1	Feb-05	repeat	Cardiovascular disorder (Cardiac)	H	11851.5	0	441.44 (798.52)	0.037
botulinum toxin (M03AX01)	Dec-93	S	4	Jun-07	first	Muscular weakness (Nervous)	F	25	↑	-0.75 (5.04)	-0.030
lamotrigine[1] (N03AX09)	Jan-96	S	3	Oct-05	first	Drug effect decreased (General)	O	688	↑	51.43 (35.65)	0.075
topiramate (N03AX11)	Jun-99	S	3	Oct-01	first	Oculomucocutaneous syndrome (Eye)	D	142	0	-6.84 (40.99)	-0.048
levetiracetam (N03AX14)	Sep-00	S	3	Nov-07	first	Incorrect dose administered (Injury)	O	701	↑	38.50 (22.21)	0.055
paroxetine[1] (N06AB05)	Jun-91	GP	2	Jan-06	first	Maternal drugs affecting foetus (Injury)	D	10451	0	432.11 (713.28)	0.041
venlafaxine (N06AX16)	Dec-97	GP	1	Sep-03	first	Suicidal ideation (Psychiatric)	O	4222.5	0	443.36 (288.97)	0.105
galantamine (N06DA04)	Jul-03	S	2	Oct-05	first	Death (General)	F	232	↑	-17.31 (29.42)	-0.075
salbutamol (R03AC02)	Dec-73	GP	4	May-07	first	Myocardial ischaemia (Cardiac)	H	53595.5	0	-6126.38 (3744.96)	-0.114

* The two DHPCs issued for nelfinavir were issued close in time and were therefore treated as a single intervention and analysed together. The first DHPC was taken as the time point of intervention.

Legend: DHPC: Direct Healthcare Professional Communication; **INN:** International Proprietary Name: drugs with more than one DHPC in our study period are indicated by their superscript numbers; **ATC:** Anatomical Therapeutic Chemical; **Appr. Date:** Approval date; **Initial prescriber**: S = medical specialist, GP = general practitioner; **Innovativeness:** 4 = important, 3 = moderate, 2 = modest, 1 = mere pharmacological/technological; **SOC:** System Organ Class; **Type of serious safety issue** = F = Death (fatal), H = Hospitalization, D = Disability/Incapacity, O = other; **Rx:** Medical prescription. **Median Rx before** = median number of Rx in the 12 months pre DHPC; **Trend =** Trend in use pre DHPC: ↑ = increasing, 0 = unchanged, ↓ = decreasing; **Absolute change in new drug use** = Change in absolute number of new drug use as determined through interrupted time series analyses; **SE**: standard error (of coefficient of Absolute change in new drug use); **Relative change in new drug use** = Absolute change in new drug use divided by the Median Rx before (Outcome measure).

Part 2

Towards optimisation of the impact of safety-related regulatory action:

a focus on Direct Healthcare Professional Communications.

Chapter 5

Healthcare professionals' self-reported experiences and preferences related to Direct Healthcare Professional Communications. A survey conducted in the Netherlands.

Sigrid Piening[1]
Flora M. Haaijer-Ruskamp[1]
Pieter A. de Graeff[1,2]
Sabine M.J.M. Straus[2,3]
Peter G.M. Mol[1,2]

Drug Safety 2012 35:11 (1061-1072)

[1] Department of Clinical Pharmacology, University of Groningen, University Medical Center, Groningen, the Netherlands
[2] Dutch Medicines Evaluation Board, The Hague, the Netherlands
[3] Medical Informatics, Erasmus Medical Center, Rotterdam, the Netherlands

Abstract

Background: In Europe, Direct Healthcare Professional Communications (DHPCs) are important tools to inform healthcare professionals of serious, new drug safety issues. However, this tool has not always been successful in effectively communicating the desired actions to healthcare professionals.

Objective: The aim of this study was to explore healthcare professionals' experiences and their preferences for improvement of risk communication, comparing views of general practitioners (GPs), internists, community pharmacists and hospital pharmacists.

Methods: A questionnaire was developed and pilot tested to assess experiences and preferences of Dutch healthcare professionals with DHPCs. The questionnaire and two reminders were sent to a random sample of 3488 GPs, internists and community and hospital pharmacists in the Netherlands. Descriptive statistics were used to describe demographic characteristics of the respondents. Chi squares, ANOVAs and the Wilcoxon signed rank test were used, when appropriate, to compare healthcare professional groups.

Results: The overall response rate was 34% (N=1141, ranging from 24% for internists to 46% for community pharmacists). Healthcare professionals trusted safety information more when provided by the Dutch Medicines Evaluation Board (MEB) than by the pharmaceutical industry. This was more the case for GPs than for the other healthcare professionals. Respondents preferred safety information to be issued by the MEB, the Dutch Pharmacovigilance Center or their own professional associations. The preferred alternative channels of drug safety information were e-mail, medical journals and electronic prescribing systems.

Conclusions: Safety information of drugs does not always reach healthcare professionals through DHPCs. To improve current risk communication of drug safety issues, alternative and/or additional methods of risk communication should be developed using electronic methods and medical journals. Moreover, (additional) risk communication coming from an independent source such as the MEB should be considered. Special effort is needed to reach GPs.

Introduction

At the time of market entry, the safety profile of a drug is incomplete due to inherent and known shortcomings of pre-marketing clinical trials.[1] Recent studies have shown that 10–14% of medicinal products require a Direct Healthcare Professional Communication (DHPC in the EU; Dear Healthcare Professional letter in the US) or 'Dear Doctor' letter (hereafter referred to as a DHPC) to inform healthcare professionals of newly identified risks within the first 3 years of market approval.[2,3]

Effective risk communication is essential to prevent or minimize harm. Evaluation of communication about cisapride and selective serotonin re-uptake inhibitors (SSRI) has shown that it is not always possible to achieve desired actions by healthcare professionals through risk communication. After safety warnings were issued announcing that the use of certain medications in combination with cisapride could cause severe cardiovascular problems, prescribing of cisapride with contraindicated medication continued, leading to its market withdrawal.[4,5] Although the SSRI warnings were only aimed at reducing new prescriptions in adolescents, unintended decreases in SSRI prescribing in adults were also observed.[6-8]

Currently, the paper-based DHPC is a major tool in risk communication of drug safety issues. In the EU, DHPCs are sent to pre-specified target groups of healthcare professionals by the pharmaceutical industry as commissioned by the European Medicines Agency and national authorities.[9]

Since effectiveness of risk communication depends largely on trust in the source of the information,[10] it is important to evaluate how different sources are perceived by healthcare professionals. In addition, evaluation of the effectiveness of risk minimization measures will become mandatory in the EU with the new pharmacovigilance legislation that came into force in July 2012.[11,12]

To optimize current risk communication methods and to improve implementation of any necessary actions into clinical practice, it is important to have good insight into the preferences of healthcare professionals. A tailor-made approach that incorporates preferences of different healthcare professional groups may facilitate the uptake of the risk information as well as implementation of the desired actions.[13] To date, little information is available on preferences of different healthcare professional groups. The aim of this study was to explore healthcare professionals' experiences and their preferences for risk communication of safety issues of medicines, comparing the views of GPs, internists and community and hospital pharmacists.

Methods

Questionnaire Development

An explorative literature search did not result in any validated questionnaires that could be used in our study. Hence, a questionnaire with open ended and closed questions was developed using the 'knowledge, attitudes, behaviour' framework introduced by Cabana et al.[14]

The attitude of healthcare professionals towards risk information was assessed with a number of statements (**Table I**). All attitude-related statements were rated on a 5-point Likert scale ranging from (1) strongly disagree to (5) strongly agree.

Table 1. Questionnaire overview[a]

Section/Question		Answer categories
Attitude		
1.	I think information about drug safety is important.	1: Strongly disagree – 5: strongly agree.
2.	It takes too much time to remain up to date on new drug safety issues.	1: Strongly disagree – 5: strongly agree.
3.	I think the MEB is knowledgeable about drugs.	1: Strongly disagree – 5: strongly agree.
4.	I think information from the MEB is trustworthy.	1: Strongly disagree – 5: strongly agree.
5.	I think the pharmaceutical industry is knowledgeable about drugs.	1: Strongly disagree – 5: strongly agree.
6.	I think information from the pharmaceutical industry is trustworthy.	1: Strongly disagree – 5: strongly agree.
Knowledge		
7.	Have you ever seen a DHPC?	Yes. No, I have heard of DHPCs, but I have never seen one. No, I have never heard of DHPCs.
8.	Do you read the DHPCs you receive?	No, I do not read any letters from the pharmaceutical industry, either in an orange hand envelope[b] or not. Yes, if they contain safety information that is important to me. Yes, only if they are sent in an orange hand envelope. Yes, only when the envelope indicates it contains important, non-commercial information. Yes, I read all letters from the pharmaceutical industry.
9.	Do you visit the MEB website for specific information on drug safety issues?	Never, I never heard of the MEB. Never, I did not know the MEB had a website. Never, I did know the MEB has a website. Yes, every 6 months. Yes, monthly. Yes, weekly. Yes, daily. Other, namely…

Table 1. Continued

Section/Question		Answer categories
10.	Are you aware of the safety issues of the following drugs for which information was sent in 2007/ 2008? (rimonabant; moxifloxacine; clopidogrel; etoricoxib)	Yes. No
11.	If yes; how did you receive this information? (DHPC; Website MEB; Media; Specialist journal; electronic mailing/internet; other, namely.)	Yes. No - Several answers possible.
Behavior		
12.	Can you estimate in which percentage of the received DHPCs you undertook action (e.g. adjusting therapy, inform colleagues, discuss with patient)?	Visual analogue scale ranging from 0% to 100%.
Preferences for alternative methods		
13.	What do you think of the current method (DHPC) with which you are informed of new drug safety issues?	1: Very poor – 10: very good.
14.	How useful do you consider repetition is of the safety information (e.g. repetition of the letter or e-mail)?	1: not at all useful – 10: very useful.
15.	How useful do you consider receiving safety information is through several methods at the same time (e.g. both postal and by e-mail)?	1: not at all useful – 10: very useful.
16.	Which of the following information channels do you think are suitable for fast information about new drug safety issues? (e-mail; text message; twitter; electronic newsletter; medical journals; RSS feed; computerized prescription system)	1: Not all useful – 10: very useful. Separately rated for each channel.
17.	Which of the following senders do you think are suitable for fast information about new drug safety issues? (physician/pharmacist; professional association; Lareb; pharmacotherapy meetings; media; drug compendium)	1: Not at all useful – 10: very useful. Separately rated for each sender.
18	Are you willing to provide the MEB with your e-mail address and/or mobile phone number to receive specific information about drug safety issues?	Yes, but only my e-mail address Yes, but only my mobile phone number Yes, both my e-mail address and my mobile phone number No

a Eighteen of the 25 questions posed in the survey are represented. Seven questions are not included here as they did not provide directly relevant information or they produced responses that demonstrated the so-called 'halo effect'. **b** Orange hand envelope: safety issues requiring immediate action (e.g. in case of contaminated batches of drugs) are sent in envelopes with an orange hand printed on them, to attract extra attention of the healthcare professional.
DHPC = Direct Healthcare Professional Communication; **Lareb** = Netherlands Pharmacovigilance Center; **MEB** = Dutch Medicines Evaluation Board; **RSS** = Really Simple Syndication.

The healthcare professionals were then asked various knowledge-related questions, and were presented with four specific drugs with safety issues (rimonabant and depression, moxifloxacin and skin reactions and hepatoxicity, clopidogrel and interaction with proton pump inhibitors, etoricoxib and hypertension).[15] These four drugs were chosen because DHPCs regarding these issues were sent to all groups of healthcare professionals included in this study within the 23 months preceding the first questionnaire.

The respondents were asked if they were aware of these safety issues and, if so, what their source of information was (DHPC, Dutch Medicines Evaluation Board [MEB] website, lay media, medical journal, electronic mailing/internet and/or other).

With regard to the behaviour component of the questionnaire, respondents were asked in what percentage of DHPCs was action taken. Respondents rated this question using a visual analogue scale ranging from 0% to 100%.

Preferences for improved risk communication were assessed on a 10-point Likert scale ranging either from (1) very poor to (10) very good or from (1) not at all useful to (10) very useful. The respondents' preferences for alternative channels (e-mail, text message, twitter, electronic newsletters, medical journals, RSS[1] feeds and computerized prescription system) and sources (physician/pharmacist, professional association, Netherlands Pharmacovigilance Centre, MEB, pharmacotherapy meetings, media, drug compendium) of risk communication were explored using a 10-point Likert scale ranging from (1) not at all useful to (10) very useful. The most appropriate answering scale was chosen for each individual question.

The following demographic aspects were collected: specific profession, sex, period of registration as a healthcare professional, full-time or part-time employment.

Face validity of the questionnaire was evaluated by five professionals (two physicians, two pharmacists, one regulator), after which changes were made to the layout, wording and predefined answers. The questionnaire was then sent to a random sample of 50 healthcare professionals to test its feasibility. Further changes were made to improve the clarity of the questionnaire. The pilot test data were not included in the final data analysis.

Study Population

Healthcare professionals living in the Netherlands were surveyed. GPs and internists (doctors of internal medicine) were included since they prescribe a wide range of drugs and therefore have a high likelihood of dealing with risk communications of drug safety issues. Hospital and community pharmacists were included because of their central role in drug dispensing and information. Respondents were excluded if they were no longer actively working as a physician or pharmacist (n=11).

Addresses of the healthcare professionals were obtained from the Dutch Internist Association (NIV) and the Dutch Pharmacist Association (KNMP). Most (~90%) of the Dutch internists and pharmacists are members of their professional association, partly because accreditation of training is arranged within these associations. The Netherlands Institute

[1] RSS (Really Simple Syndication) feeds make it possible to see when websites have added new information, such as, for example, news headlines and press releases. RSS feeds make checking separate websites unnecessary.

for Health Services Research (NIVEL) provided a random sample of Dutch GPs. A sample size calculator[16] was used to determine the number of respondents that would be needed to obtain the appropriate sample size to result in 80% power to detect a 10% difference in healthcare professionals' ratings of individual questions.

We adjusted the sample size based on the response rates observed in the feasibility study, where response ranged from 20% to 80% for internists and community pharmacists, respectively (**Table 2**).

Table 2. Demographic characteristics of the respondents

Characteristic	Total [N (%)]	GP [N (%)]	Internist [N (%)]	Community pharmacist [N (%)]	Hospital pharmacist [N (%)]
Response					
Total[a]	1,141 (34%)	233 (33%)	410 (24%)	323 (46%)	175 (45%)
Initial mailing	686 (60%)	112 (48%)	269 (66%)	184 (57%)	121 (69%)
Reminder 1	358 (31%)	67 (27%)	137 (33%)	101 (31%)	53 (30%)
Reminder 2	97 (9%)	54 (23%)	4 (1%)	38 (12%)	1 (1%)
Pilot (N=50)	22 (44%)	6 (40%)	3 (20%)	8 (80%)	5 (50%)
Healthcare professional characteristics					
Female (4 missing)	465 (40%)	97 (42%)	141 (34%)	146 (45%)	81 (47%)
Years of professional accreditation (2 missing)					
Trainee	7 (1%)	1 (0%)	0 (0%)	5 (2%)	1 (1%)
1-5	207 (18%)	24 (10%)	87 (21%)	58 (18%)	38 (22%)
6-10	240 (21%)	47 (20%)	76 (19%)	68 (21%)	49 (28%)
11-15	173 (15%)	37 (16%)	49 (12%)	61 (19%)	26 (15%)
≥16	512 (45%)	124 (53%)	197 (48%)	130 (40%)	61 (35%)
Working part time (3 missing)	258 (22%)	78 (34%)	57 (14%)	72 (22%)	51 (29%)

a Differences in percentages may exist due to rounding.
GP= General Practitioner.

This resulted in sending questionnaires to 3488 healthcare professionals (700 randomly selected GPs, 700 randomly selected community pharmacists, all 1696 Dutch internists and all 392 hospital pharmacists) in the Netherlands in December 2009.

The anonymous questionnaire was sent with a cover letter and a prepaid return envelope. To maximize the response, a total of two reminders accompanied by the questionnaire were sent at month 1 and 2 after the initial mailing.[17]

Data Entry and Analysis

Data were entered by three data entry assistants using structured data entry forms. Data entry was checked by examining duplicate entries of 10% of all returned questionnaires for errors. The duplicate data entry resulted in less than 0.1% error in the entered variables. The majority of the data entry errors (83%) were related to questions 10 and 11 (**Table 1**). All entries of these two questions were therefore compared with the original returned questionnaires and corrected when appropriate.

Assuming that the respondents who returned the questionnaire only after a reminder were most comparable to non-responders, sensitivity analyses were performed to explore possible differences between initial and late responders, on the main questions of trust, knowledge and preferences. Descriptive statistics were used to describe demographic characteristics of the respondents. Chi squares, ANOVAs and the Wilcoxon signed rank test were used when appropriate to compare healthcare professional groups. Data were analysed using SPSS 16.0 software (SPSS, Inc., Chicago, Illinois, USA).

Results

The questionnaire and reminders were sent to 3488 healthcare professionals in the Netherlands in December 2009 and January 2010, resulting in an overall response rate of 34% (N=1141; ranging from 24% for internists to 46% for community pharmacists; **Table 2**). Most healthcare professionals who returned our questionnaire were male (60%), working full-time (78%) and registered as a healthcare professional for 15 years or fewer (55%).

Attitude

The majority (mean ± SD) of the healthcare professionals considered risk information of medicinal products to be important (4.67 ± 0.6), ranging from an average of 4.55 ± 0.5 reported by the GPs to 4.77 ± 0.5 by the hospital pharmacists ($p \leq 0.0001$). Most healthcare professionals did not have an opinion, or had a neutral attitude about the statement 'It takes too much time to remain up to date on new drug safety issues' (2.56 ± 0.9). The GPs more often reported that remaining up to date took too much time (2.80 ± 1.0), while the community pharmacists indicated this the least often (2.39 ± 0.9; $p \leq 0.001$).

The healthcare professionals considered both the MEB and the pharmaceutical industry knowledgeable about drugs (4.06 ± 0.7 and 3.91 ± 0.7, respectively), but trusted the risk information provided by the MEB more (4.13 ± 0.6 and 2.70 ± 0.8, respectively; $p \leq 0.001$; **Figure 1**). In particular, the GPs thought that information provided by the MEB was significantly more trustworthy than information provided by the pharmaceutical industry ($p \leq 0.001$).

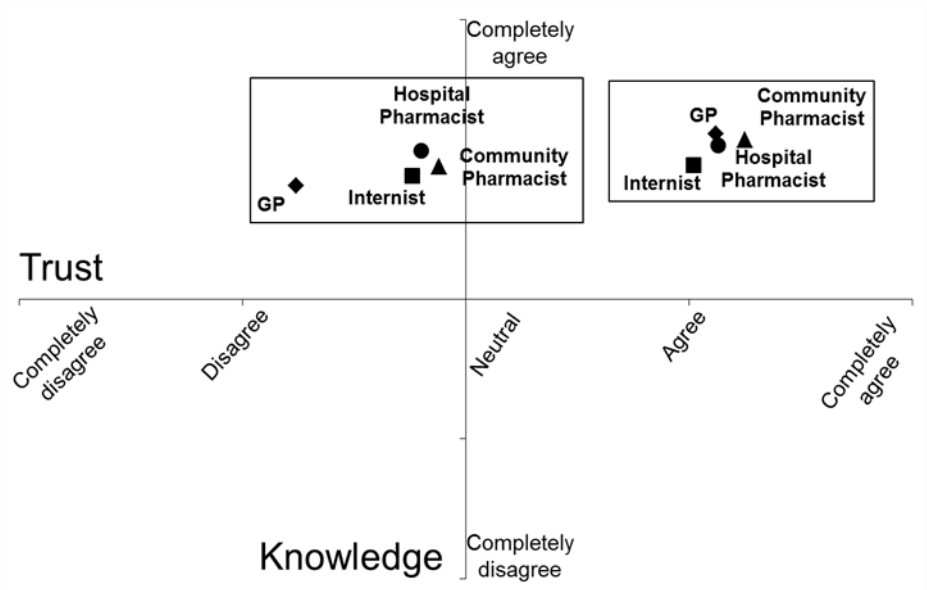

Figure 1. Trust and knowledge attributed to the Dutch MEB/ pharmaceutical industry
GP= General Practitioner; **MEB=** Medicines Evaluation Board.

Knowledge

Sixteen percent of the healthcare professionals (ranging from 5% of the hospital pharmacists to 28% of the GPs; p≤0.001) were not familiar with DHPCs. The majority (58%) of the healthcare professionals indicated that they read only the DHPCs that contained information that was relevant to them, and 30% of the community pharmacists read all letters they received from the pharmaceutical industry (p≤0.001).

Four specific drugs with safety issues were presented to the healthcare professionals (rimonabant, moxifloxacin, clopidogrel and etoricoxib). Most healthcare professionals indicated that they were aware of all four safety issues, ranging from 56% for the etoricoxib issue to 88% for the clopidogrel issue (**Figure 2**). The pharmacists were better informed than the physicians (p≤0.001) for all safety issues except etoricoxib. In the etoricoxib case, primary care healthcare professionals (GPs and community pharmacists) were more aware of the safety issue (67% and 71%, respectively) than the secondary care healthcare professionals (internists and hospital pharmacists; 40% and 51%, respectively; p≤0.001). Knowledge of the four safety issues was mostly obtained from professional journals (59%) and DHPCs (49%), while the MEB website was rarely indicated (5%) as the information source.

Sixty-four per cent of the respondents indicated that they never visited the MEB website to search for more information about safety issues. Seven percent of the

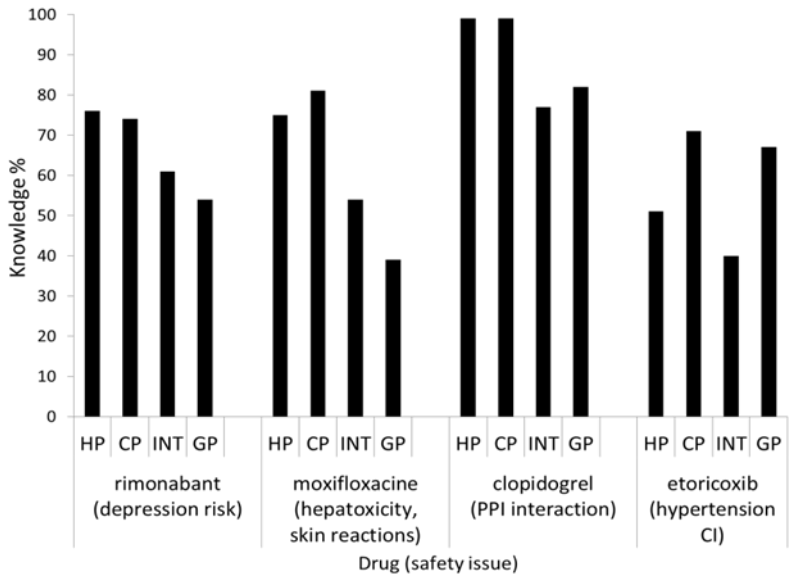

Figure 2. Healthcare professionals' knowledge of safety issues of four drugs.
CP = Community pharmacist; **GP**= general practitioner; **HP**= hospital pharmacist; **INT**= internist; **PPI**= proton pomp inhibitor.

healthcare professionals were not aware of the existence of the MEB. Only 6% of the respondents visited the website weekly and only 1% did so daily. Hospital and community pharmacists were more aware of the MEB and visited the MEB website more often than internists and GPs (p≤0.001), although 38% of the pharmacists visited the website only monthly or 6 monthly.

Behaviour

The healthcare professionals reported to have taken action (e.g. adjusting therapy, informing colleagues, discussion with patient) in response to 29% of the DHPCs, ranging from 23% of internists to 37% of community pharmacists (p≤0.001).

Preferences for Improved Risk Communication

Satisfaction with the current way of risk communication was rated as mean 6.9 (SD ±1.9) out of 10, ranging from 6.0 ± 2.1 on average by GPs to 7.6 ± 1.4 by community pharmacists (p≤0.001). Repetition of the risk communication as well as information coming from several sources simultaneously was rated as moderately useful (5.8 ± 2.4; and 6.3 ± 2.4, respectively). The open- ended question regarding which specific combination was preferred yielded responses from 494 healthcare professionals (multiple answers were

given). Predominantly, a combination of the paper-based DHPC with an e-mail was suggested (n=184). Receiving risk information via e-mail only was indicated 91 times and via the paper-based DHPC only was indicated 41 times. The preferred alternative channels of risk information were e-mail, medical journals and electronic prescribing systems. The preferences for these three channels varied across the four healthcare professional groups (**Table 3**).

RSS feeds, text messages and twitter were not favoured methods. According to the healthcare professionals, risk communication should preferably be issued by the MEB, the

Table 3. Preferred alternative drug safety information channels and sources [mean (SD)][a]

	GP	Internist	Community Pharmacist	Hospital Pharmacist	Total	p-Value
Channel						
E-mail	7.16 (2.5)	7.24 (2.5)	8.07 (1.8)	8.09 (2.0)	7.59 (2.3)	p≤0.001[b]
Text message	232 (1.9)	2.13 (1.7)	3.05 (2.4)	2.41 (2.3)	2.47 (2.1)	p≤0.001[b]
Twitter	1.72 (1.2)	1.65 (1.2)	2.13 (1.8)	1.68 (1.4)	1.81 (1.4)	p≤0.001[b]
Electronic newsletter	5.66 (2.9)	5.99 (2.8)	6.53 (2.4)	6.37 (2.8)	6.14 (2.7)	p≤0.001[b]
Medical journals	7.32 (2.2)	7.85 (1.7)	7.32 (2.0)	7.15 (2.2)	7.49 (2.0)	p≤0.001[b]
RSS feeds	3.44 (2.4)	3.74 (2.7)	4.05 (2.7)	5.06 (3.0)	3.98 (2.8)	p≤0.001
Computerised prescription system	7.83 (2.2)	6.52 (3.1)	7.45 (2.4)	7.03 (2.6)	7.14 (2.7)	p≤0.001[b]
Source						
Physician (by pharmacists)	NA	NA	4.76 (2.5)	3.90 (2.4)	4.46 (2.5)	p≤0.001[b]
Pharmacist (by physicians)	8.14 (1.8)	6.90 (2.4)	NA	NA	7.35 (2.3)	p≤0.001[b]
Professional association	7.60 (1.9)	7.98 (1.7)	8.27 (1.4)	7.93 (1.9)	7.98 (1.7)	p≤0.001
Lareb	7.82 (1.8)	7.98 (1.8)	8.37 (1.2)	8.00 (1.8)	8.06 (1.7)	p≤0.001[b]
MEB	7.70 (1.8)	7.94 (1.6)	8.38 (1.2)	8.64 (1.2)	8.13 (1.5)	p≤0.001[b]
Pharmacotherapy meetings	7.63 (2.1)	4.94 (2.3)	6.06 (2.4)	4.55 (2.3)	5.76 (2.5)	p≤0.001[b]
Media	3.90 (2.2)	3.90 (2.3)	3.78 (2.3)	3.42 (2.2)	3.79 (2.2)	p=0.101
Drug Compendium	7.41 (2.1)	7.19 (22)	6.29 (2.6)	5.40 (2.8)	6.71 (2.5)	p≤0.001[b]

a All channels and sources were rated on a 10-point Likert scale ranging from (1) not at all useful, to (10) very useful. **b** Indicates significant (p≤0.05) differences in preference between the four healthcare provider groups in the ANOVA analysis.
GP= general practitioner; **Lareb**= Dutch Pharmacovigilance Centre; **MEB=** Dutch Medicines Evaluation Board; **NA**= not applicable; **RSS**= Really Simple Syndication.

Dutch Pharmacovigilance Center (Lareb) or their own professional association (**Table 3**). The media were rated as the least preferable source of risk communication.

Sensitivity analyses showed significant differences between responders to the initial mailing and the two subsequent reminders in only two preference variables. In those two cases, the late responding physicians rated safety information coming from pharmacists higher than did physicians responding to the initial mailing ($p=0.007$). The late responding healthcare professionals also rated the pharmacotherapy meetings higher than did early responding healthcare professionals ($p \leq 0.001$).

Discussion

Although the responding healthcare professionals considered risk information on drug safety issues to be important, a substantial group was not familiar with the DHPC as a tool for risk information. Pharmacists appeared to be more aware of, and more responsive to, safety issues than physicians, particularly GPs. The majority of the healthcare professionals preferred to receive drug safety information from an independent source such as the MEB or their own professional association than from DHPCs. Moreover, most healthcare professionals preferred to receive the information through medical journals or electronically, for example, by e-mail or electronic (prescribing) systems.

Fifteen percent of the respondents had never heard of or seen a DHPC. This percentage is similar to the results from an earlier study performed in the US, where 18% of the respondents indicated they had never seen a DHPC.[18] In contrast, other studies reported higher percentages of respondents with knowledge of drug safety warnings.[19-21]

Awareness of the specific safety issues and reported action in response to a DHPC was higher among pharmacists. In addition, they visited the MEB website more frequently than physicians. This might be explained by the focus of pharmacists on pharmacotherapy and drug risks, while for physicians this aspect might have a lower priority. This is supported by the finding that the physicians rated 'keeping up to date on risk information' as time consuming more often than pharmacists.

Awareness of the four safety cases ranged from moderate for the etoricoxib issue (55%) to high for the clopidogrel issue (85%). Pharmacists were better informed than physicians, except in the etoricoxib case, where the GPs and community pharmacists were more aware of the safety issue than hospital pharmacists and internists. Etoricoxib is mainly prescribed and dispensed in primary care, which could explain this finding. Only in the moxifloxacin case was the DHPC indicated as the main risk information source. In the other three cases, the information was mainly obtained from professional journals. This is in line with earlier research, which found that healthcare professionals mainly use sources of safety information other than the DHPC.[22,23]

The respondents reported having taken action in relation to 29% of the DHPCs they received. This percentage is higher than that reported by Canadian healthcare professionals, which ranged from 2% adjusting their prescribing to 16% forwarding the DHPC to other healthcare professionals.[19] In other studies, higher percentages of action were reported by healthcare professionals, e.g. changes in prescribing behaviour of 80% related to an antidepressants black-box warning,[20] and 40% related to a long-acting beta agonists black-box warning.[21] It should be noted that not all DHPCs require immediate action from all healthcare professionals.

The preference for receiving drug safety information from an independent organization is in line with findings of earlier studies. Physicians in the UK and the US prefer independent sources (e.g. medical journals and colleagues) over commercial (e.g. pharmaceutical companies) and third-party sources (e.g. general media).[22,23] The respondents in our study, especially the GPs, indicated they would have more trust in drug safety information coming from the MEB than from the pharmaceutical industry. Trust in both the sender and the information itself plays an essential role in successful risk communication.[24] It is suggested that inadequate risk communication may be caused by insufficient trust in the institutions that are responsible for risk management.[10]

E-mail and electronic prescribing/dispensing systems, the preferred channels of respondents, could prove to be good channels of risk communication because of their user-friendliness. Such an e-mail would preferably consist of a short summary of the drug safety issue and the recommendations to the healthcare professional on how to manage the safety issue. A link to the DHPC and to background information on the drug safety issue could be incorporated in the e-mail. The header of the e-mail should clearly indicate the safety issue and the drug in question. Presently, the MEB already offers an e-mail service to voluntary subscribers. In our survey, 84% of the respondents indicated they were willing to provide the MEB with their e-mail address to receive such an e-mail. The physicians, especially the GPs, rated pharmacists quite highly as an alternative source of safety information. Information from professional associations was also a preferred alternative. A more active involvement of these groups as intermediaries in the risk communication process could be an important additional step to strengthen this process.

One of the aims of DHPCs is to rapidly inform healthcare professionals when a safety issue is identified. However, it should be noted that incorporating warnings of safety issues into electronic prescribing/dispensing systems requires some time, which could cause unnecessary harm to patients. E-mail could prove to be more useful in rapidly informing healthcare professionals, and incorporating warnings in electronic prescribing/dispensing systems may additionally be applied. The respondents indicated they would not prefer to receive safety information through methods such as twitter, RSS

feeds and text messaging, even though communication through these methods could be implemented relatively easily. Since these are relatively novel methods, it may be worthwhile to keep track of how the use of and preference for these methods develop.

A substantial number of respondents indicated that they would prefer to receive the safety information via both the paper-based DHPC and an additional e-mail. However, repetition of the risk information as well as receiving information simultaneously from several sources was rated as only moderately useful. This apparent discrepancy indicates that a fine balance seems to exist between a preference for receiving the information through various methods and an overload of information. This is important to note, since such an overload could easily cause 'warning fatigue', resulting in healthcare professionals not taking notice of risk communications.

The limited awareness that healthcare professionals had of the MEB and the MEB website seems to be comparable to familiarity with other national authorities. In the UK for example, approximately 20% of the healthcare professionals indicated they were aware of the Medicines and Healthcare products Regulatory Agency (MHRA).[23] In Canada, 38% of the healthcare professionals were familiar with the drug safety advisories on the Health Canada website, but only 9% of the healthcare professionals visited this website to retrieve new drug safety information.[19] A focus group study performed in Canada indicated that the 'reporting authority is perceived as a virtual and remote entity'.[25] Although it appears that healthcare professionals see a clear role for regulating authorities in communicating safety issues, their visibility amongst healthcare professionals should be improved.

Strengths and Limitations

This is one of the first studies assessing healthcare professionals' opinions of DHPCs. A sizable group of 1141 healthcare professionals, both pharmacists and physicians, were included in our survey. We used a pre-tested questionnaire, preserving the anonymity of the respondents to reduce the possibility of socially desirable answers.

Limitations to this study include a fairly low response rate, with only 34% of the healthcare professionals responding. This is comparable to other surveys amongst healthcare professionals, especially amongst physicians.[20,21,26] Still, the low response may have biased our results in that healthcare professionals who are unaware of, or not interested in, DHPCs could be underrepresented in our sample. This might mean that, in reality, even fewer healthcare professionals are aware of DHPCs and safety issues, which underlines the need for improvements in current risk communication. We were unable to analyse any characteristics of the non-responders due to the anonymous nature of the questionnaire. We can only report that our sample is representative for the Dutch setting

in terms of sex,[27] and the percentage of GPs who work part-time.[28] We found no significant differences between early and late responders, except for two preference variables. It is possible that the non-responders have different preferences with regard to the pharmacists and pharmacotherapy meetings than the responders. We can conclude that, apart from these two variables, our results are, in all likelihood, not affected by non-response bias. Due to the anonymous nature of the questionnaire, it is possible that healthcare professionals might have responded to both the initial mailing as well as the reminders. However, in the cover letters of the reminders, we explicitly stated that these mailings concerned reminders, which should be ignored if the questionnaire had already been returned. Since the reminders were sent within a month of the previous mailing, and because of the specific topic, we assume that the respondents would have remembered filling out the earlier questionnaire. This was underlined by the fact that some respondents actually notified us about this. It should be noted that 'action in response to DHPCs' was a self-reported measure. Respondents may have had difficulties remembering the number of DHPCs they received for which they actually took action, leading to possible recall bias. We cannot rule out that some healthcare professionals may perceive a DHPC as information from the pharmaceutical industry, despite our explanation in the questionnaire that a DHPC is issued on request from and in collaboration with the MEB. This might have influenced their responses to several questions, for example questions 8 (reading the DHPCs) and 13 (satisfaction with the current communication method).

Conclusions

Healthcare professionals consider staying up to date on new drug safety issues important, although a fair proportion were not aware of the DHPC as a risk communication tool. Those who were aware rated this risk communication method as reasonable, but valued electronic methods as alternative or additional risk communication channels. In line with this, healthcare professionals indicated mainly other channels as the source for their knowledge of some recent drug safety issues. Our study also showed that healthcare professionals had greater trust in the MEB than in industry as a source of drug safety information and that they would prefer to be informed through independent organizations.

Therefore, current risk communication of medicinal products should be improved, preferably by using electronic methods, including e-mail and electronic prescription systems, and/or medical journals. Moreover, (additional) safety information should come from an independent source such as the MEB to optimize credibility. The results of this study indicate that additional efforts are needed to ensure that the safety information reaches healthcare professionals.

Acknowledgements

The authors would like to thank Michelle Pena for her contribution to an earlier version of the article. This study was supported by an unconditional grant from the Dutch Medicines Evaluation Board (CBG-MEB). The authors, who are also (part-time) employees of the MEB (Pieter de Graeff, Sabine Straus and Peter Mol), state that the opinions presented in this paper are their own and do not necessarily reflect that of the MEB. All authors report that they do not have any conflicts of interest.

References

1 Stricker BC, Psaty BM. Detection, verification, and quantification of adverse drug reactions. Br Med J 2004 07;329(7456):44-47.

2 Giezen TJ, Mantel-Teeuwisse AK, Straus SMJM, Schellekens H, Leufkens HGM, Egberts ACG. Safety-related regulatory actions for biologicals approved in the United States and the European Union. J Am Med Assoc 2008 10;300(16):1887-1896.

3 Arnardottir AH, Haaijer-Ruskamp FM, Straus SMJ, Eichler H-, de Graeff PA, Mol PGM. Additional safety risk to exceptionally approved drugs in Europe? Br J Clin Pharmacol 2011 72(3):490-499.

4 Weatherby LB, Walker AM, Fife D, Vervaet P, Klausner MA. Contraindicated medications dispensed with cisapride: Temporal trends in relation to the sending of 'Dear Doctor' letters. Pharmacoepidemiol Drug Saf 2001 10(3):211-218.

5 Guo JJ, Curkendall S, Jones JK, Fife D, Goehring E, She D. Impact of cisapride label changes on codispensing of contraindicated medications. Pharmacoepidemiol Drug Saf 2003 12(4):295-301.

6 Gibbons RD, Brown CH, Hur K, Marcus SM, Bhaumik DK, Erkens JA, et al. Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. Am J Psychiatry 2007 164(9):1356-1363.

7 Olfson M, Marcus SC, Druss BG. Effects of food and drug administration warnings on antidepressant use in a national sample. Arch Gen Psychiatry 2008 65(1):94-101.

8 Valuck RJ, Libby AM, Orton HD, Morrato EH, Allen R, Baldessarini RJ. Spillover effects on treatment of adult depression in primary care after FDA advisory on risk of pediatric suicidality with SSRIs. Am J Psychiatry 2007 164(8):1198-1205.

9 European Commission. Volume 9A of the rules governing medicinal products in the European Union. Guidelines on Pharmacovigilance for medicinal products for human use. 2008; Available at: http://ec.europa.eu/health/files/eudralex/vol-9/pdf/vol9a_09-2008_en.pdf. Accessed March 24, 2011.

10 Slovic P. Perceived risk, trust, and democracy. Risk Anal 1993 13(6):675-682.

11 The European Parliament and The European Council. REGULATION (EU) No 1235/2010. 2010; Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0001:0016:EN:PDF. Accessed January 4, 2010.

12 The European Parliament and The European Council. DIRECTIVE 2010/84/EU. 2010; Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0074:0099:EN:PDF. Accessed January 4, 2011.

13 Grol R, Grimshaw J. From best evidence to best practice: Effective implementation of change in patients' care. Lancet 2003 2003/10;362(9391):1225-1230.

14 Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud P-C, et al. Why don't physicians follow clinical practice guidelines?: A framework for improvement. J Am Med Assoc 1999 10;282(15):1458-1465.

15 Dutch Medicines Evaluation Board. Direct Healthcare Professional Communications. 2012; Available at: http://www.cbg-meb.nl/CBG/en/human-medicines/pharmacovigilance/DHPC/default.htm. Accessed 10 February, 2012.

16 Raosoft I. Sample size calculator. 2004; Available at: http://www.raosoft.com/samplesize.html. Accessed September 17, 2009.

17 Edwards PJ, Roberts I, Clarke MJ, DiGuiseppi C, Wentz R, Kwan I, et al. Methods to increase response to postal and electronic questionnaires. Cochrane Database Syst Rev 2009 (3).
18 Lee LY, Kortepeter CM, Willy ME, Nourjah P. Drug-risk communication to pharmacists: assessing the impact of risk-minimization strategies on the practice of pharmacy. J Am Pharm Assoc 2008 48(4):494-500.
19 Health Canada. Public opinion survey on key issues pertaining to post-market surveillance of marketed health products in Canada. 2004; Available at: http://www.hc-sc.gc.ca/dhp-mps/pubs/medeff/_res-rec/2004-decima_2003_final_rep-rapp/index-eng.php. Accessed June 22, 2011.
20 Cheung A, Sacks D, Dewa CS, Pong J, Levitt A. Pediatric prescribing practices and the FDA black-box warning on antidepressants. J Dev Behav Pediatr 2008 29(3):213-215.
21 Karpel JP, Peters JI, Szema AM, Smith B, Anderson PJ. Differences in physicians' self-reported knowledge of, attitudes toward, and responses to the black box warning on long-acting beta-agonists. Ann Allergy Asthma Immunol 2009 103(4):304-310.
22 Morrato EH, Curbow B, Crum RM, Nowels C, Feinleib M. Communicating drug risk to physicians: Challenges and opportunities. Int J Risk Saf Med 2008 20(3):143-154.
23 Medicines and Healthcare products Regulatory Agency / Ipsos Mori. Risks and benefits of medicines and medical devices - Perceptions, communication and regulation. Report on quantitative research among health professionals. 2006; Available at: http://www.mhra.gov.uk/Publications/Corporate/Research/index.htm. Accessed July 8, 2011.
24 Berry DC. Risk, Communication and Health Psychology. 1st ed. Berkshire United Kingdom: Open University Press; 2004.
25 Nichols V, Theriault-Dube I, Touzin J, Delisle J-, Lebel D, Bussieres JF, et al. Risk perception and reasons for noncompliance in pharmacovigilance: A qualitative study conducted in Canada. Drug Saf 2009 32(7):579-590.
26 Ko Y, Malone DC, Skrepnek GH, Armstrong EP, Murphy JE, Abarca J, et al. Prescribers' knowledge of and sources of information for potential drug-drug interactions: A postal survey of US prescribers. Drug Saf 2008 31(6):525-536.
27 Dutch Ministry of Health, Welfare and Sports. BIG register. Cijfers. (Only available in Dutch). 2011; Available at: http://www.bigregister.nl/overbigregister/cijfers/. Accessed February 7, 2012.
28 Netherlands Institute for Health Services Research (NIVEL). Beroepen in de gezondheidszorg. Databank. 2011; Available at: http://www.nivel.nl/databank. Accessed 30 May, 2012.

Chapter 6

The additional value of an e-mail to inform healthcare professionals of a drug safety issue.

Sigrid Piening[1]
Pieter de Graeff[1,2]
Sabine Straus[2,3]
Flora Haaijer-Ruskamp[1]
Peter Mol[1,2]

Drug Safety 2012 36:9 (723-731)

[1] Dept. of Clinical Pharmacology, University of Groningen, University Medical Center Groningen, the Netherlands
[2] Dutch Medicines Evaluation Board, Utrecht, the Netherlands
[3] Dept. of Medical Informatics, Erasmus Medical Center, Rotterdam, the Netherland

Abstract

Background: The usefulness and the impact of Direct Healthcare Professional Communications (DHPCs, or 'Dear Doctor letters') in changing the clinical behaviour of physicians have been debated. Changes in the current risk communication methods should preferably be based on the preferences of the healthcare professionals, to optimize the uptake of the message.

Objective: The aim of this study was to assess whether safety issues are communicated more effectively with an additional e-mail sent by the Dutch Medicines Evaluation Board (MEB) than with the DHPC only.

Methods: A randomized controlled trial was conducted amongst ophthalmologists and hospital pharmacists in the Netherlands, who were the target group of a DHPC that was issued for pegaptanib, a drug that is administered intra-ocularly in patients with macular degeneration. The intervention group (N=110) received the pegaptanib DHPC, as well as the MEB e-mail. The control group (N=105) received the traditional paper-based DHPC only. Two weeks later, the study population received an invitation to fill out an online questionnaire. Questions were asked about the respondents' knowledge and attitude regarding the pegaptanib issue, and any action they had consequently taken. Additional questions were asked about their satisfaction with the DHPC and the e-mail, and their preferred source of such information.

Results: Forty respondents (18.6%) completed the questionnaire. Eighty-one percent of the respondents in the intervention group (N=21) and 47% of the control group (N=19) correctly indicated that a serious increase in intra-ocular pressure could be caused by pegaptanib injections (Fishers' exact test, p=0.046). Nine respondents in the intervention group versus none of the control group respondents indicated that they had taken action in response to the pegaptanib safety issue (Fishers' exact test, p=0.01). The majority of both the intervention group and the control group confirmed that they would like to receive an MEB e-mail with safety information about drugs in the future (90 and 95%, respectively).

Conclusion: The results of this study indicate that an additional e-mail might strengthen the uptake of the safety information provided to healthcare professionals, who prefer to receive an e-mail from the MEB as a source of such information, as well as the DHPC. This study may serve as a starting point for new strategies to improve risk communication regarding safety issues associated with drugs and its impact on prescribing.

Introduction

The usefulness and the impact of Direct Healthcare Professional Communications (DHPCs, or 'Dear Doctor letters') in changing the clinical behaviour of physicians have been debated.[1-3] Currently, very little is known about the effect of communication efforts other than the DHPC to rapidly inform healthcare professionals about newly identified safety issues associated with drugs. Such information would provide a much needed knowledge base, in particular since evaluation of the impact of risk-minimization measures became mandatory in July 2012 in Europe, when the new European pharmacovigilance legislation[4,5] came into force. What is known, though, is that any change in the current risk communication methods should preferably be based on the preferences of the healthcare professionals, to optimize the uptake of the message.[6]

Previous research has shown that healthcare professionals prefer to receive safety information electronically and from an independent, trustworthy source.[7-12] Strengthening the safety message by repetition through different means might be very effective in getting the information across, especially when the message is similar but not identical.[13] For this reason, the Dutch Medicines Evaluation Board (MEB) has offered, from October 2010 onwards, an additional e-mail newsletter, to which interested parties can subscribe. With this e-mail, healthcare professionals are informed of drug safety issues for which a DHPC is issued.

Recently, the MEB planned to send such an e-mail in conjunction with a DHPC that was issued for pegaptanib (a drug that is administered intra-ocularly in patients with macular degeneration), as serious adverse drug reactions had occurred. The aim of this study was to assess whether safety issues are communicated more effectively with an additional e-mail than with a DHPC only, by studying the impact of this e-mail, in particular on the knowledge and action taken by the healthcare professionals, their attitude to this safety issue, and their satisfaction with this additional information. For this reason, a special questionnaire was developed.

Methods

Study Population

The study population was chosen in agreement with the target population (as stated in the communication plan of the pegaptanib DHPC), consisting of ophthalmologists and hospital pharmacists in the Netherlands (**Figure 1**).

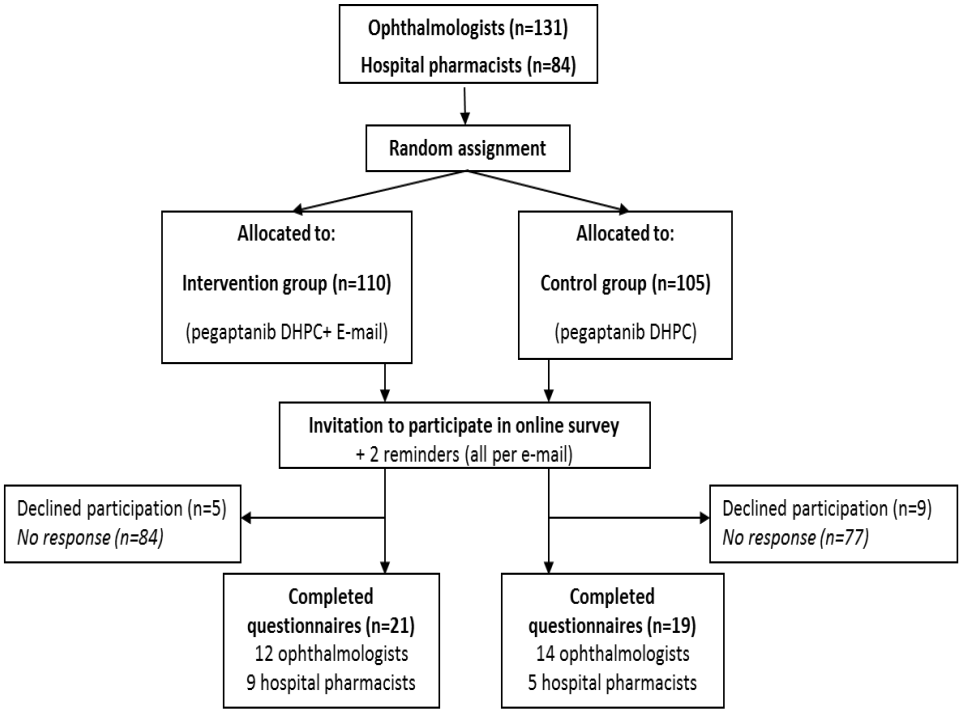

Figure 1. Study flow chart
DHPC= Direct Healthcare Professional Communication.

The study population was not selected from a list of previous subscribers to the newsletter. The e-mail addresses of the hospital pharmacists (N=84) were obtained from the Dutch Pharmacist Association (KNMP). For the e-mail addresses of ophthalmologists (N=131), the websites of Dutch hospitals were reviewed. The healthcare professionals were randomly assigned to the control group (N=105) or the intervention group (N=110). In addition to the traditional paper-based DHPC, the intervention group received the e-mail newsletter (**Figure 2**). The control group received the DHPC only. Two weeks later, both groups received an invitation by e-mail to fill in an online questionnaire (Questback EFS survey 9.0). The questionnaire could be accessed by clicking on a personalized link in the invitation e-mail. Reminders were sent 1 and 2 weeks after the original invitation, including the same personalized link.

The Study Drug

Pegaptanib was approved in January 2006 for the treatment of neovascular (wet) age-related macular degeneration in adults.[14] It should only be administered by

Figure 2. The e-mail that was sent to the intervention group
An introduction was placed on top of the Dutch Medicines Evaluation Board (MEB) e-mail, to state its purpose.

Figure 2. Continued

Translation:

SUBJECT: MEB warning – Risk information Macugen

Dear Sir, Madam,

The information below was written by the Medicines Evaluation Board, in relation to safety issues of the drug Macugen (pegaptanib). Simultaneously a letter ('Dear Doctor letter') was sent to you about this issue by the pharmaceutical company.
You are receiving this e-mail in the framework of the CORE study (UMCG) which aims to improve the current risk communication of safety issues of medicines.

Kind regards,
The CORE team

Risk information Macugen

The Medicines Evaluation Board draws your attention to the following:

RISK OF SERIOUS INCREASE OF INTRAOCULAR PRESSURE WITH INJECTION OF EXCESS VOLUME OF MACUGEN

Information from clinical trials and clinical practice has shown that there is a risk when administering pre-filled syringes with pegaptanib (Macugen). The prefilled syringes contain an excess volume. It is important that this excess volume is properly removed, and not injected the eye. Two cases were reported where this has not been done and where the anterior chamber had to be pierced to lower the pressure.

This is written by Pfizer in a letter, a so-called Direct Healthcare Professional Communication (DHPC). The letter with this important risk information is sent to ophthalmologists and hospital pharmacists in consultation with the Board of the Medicines Evaluation Board (MEB) and the Health Care Inspectorate (IGZ).

The product information for doctors and pharmacists (SmPC) is also added to this letter.
Pegaptanib is prescribed for the treatment of patients with the wet type of age-related macular degeneration (AMD). This disease affects the central part of the retina (the macula) at the back of the eye and causes loss of vision when looking straight ahead.

Identifying and analysing adverse events throughout the life cycle of a drug is called pharmacovigilance. This is a core task of the MEB. In case of urgent and/or important safety issues healthcare professionals are informed by means of a 'Direct Healthcare Professional Communication'. Click here for an overview of DHPCs.

This is the electronic newsletter of the Medicines Evaluation Board. You can respond to this newsletter via the button bottom right of the page or contact the Information and Communication Department of the MEB.

CORE = Communicating Risk Effectively; **UMCG** = University Medical Center Groningen.

ophthalmologists experienced in giving intravitreal injections.[15] Due to reports of a serious adverse drug reaction, consisting of increased intraocular pressure caused by administration of the excess volume of pegaptanib present in the pre-filled syringe, a DHPC was instigated at the EU level.[15] In the Netherlands, the DHPC was sent to all ophthalmologists and hospital pharmacists,[16] advising ophthalmologists to expel the excess volume of pegaptanib from the syringe before administration. The DHPC was accompanied by the amended Summary of Product Characteristics[17] and a visual representation of the correct administration method.[18]

Questionnaire Development

The main outcome measures of this intervention study were knowledge of the issue, the attitude towards the issue, and action taken to minimize the risk. Additionally, satisfaction with the risk communication was assessed. Since an explorative literature search did not result in any usable validated questionnaires, we developed a questionnaire (**Table 1**) using the 'knowledge, attitudes, behaviour' model of Cabana et al.,[19] representing possible barriers to physicians' adherence to guidelines.

Table 1. Questionnaire overview

Section/Question[a]		Answer categories
General		
1.	Did you receive and read the letter (DHPC) about Macugen (pegaptanib)?	1: Yes, I have received the letter and read it in detail. 2: Yes, I have received the letter and skimmed through it. 3: Yes, I have received the letter, but I have not read it. 4: No, I have not received the letter.
2.	Did you receive and read the e-mail about Macugen (pegaptanib)?	1: Yes, I have received the e-mail and read it in detail. 2: Yes, I have received the e-mail and skimmed through it. 3: Yes, I have received the e-mail, but I have not read it. 4: No, I have not received the e-mail.
Knowledge		
3.	Does it take you too much time to keep up with new drug safety issues?	1: Yes, strongly agree – 5: No, strongly disagree.

Table 1. Continued

	Section/Question*	Answer categories
4.	Can you specify which new safety issue was identified for Macugen (pegaptanib)?	1: Yes, an increased risk of retinal detachment due to administration of Macugen (pegaptanib). 2: Yes, an increased risk of an increased intraocular pressure due to administration of an excess volume of Macugen (pegaptanib). 3: Yes, an increased risk of endophthalmitis, possibly leading to panophthalmia due to administration of Macugen (pegaptanib). 4: I don't know
5.	Were you aware of the Macugen (pegaptanib) safety issue of before the DHPC and/or e-mail were sent? (Several answers possible)	1: No 2: Yes, via scientific literature 3: Yes, via my professional association 4: Yes, via colleagues 5: Yes, via the sales representative of the pharmaceutical company 6: Yes, via an e-mail newsletter 7: Yes, otherwise, namely…
6.	Can you specify which recommendation was made in connection with this safety issue?	1: Yes, remove the excess volume from the syringe before administration of Macugen (pegaptanib). 2: Yes, stop administration of Macugen (pegaptanib) at the first sign of the adverse event. 3: Yes, stop administration of Macugen preventively and switch to alternative treatment. 4: I don't know
Attitude		
7.	Do you think information about drug safety by means of DHPCs is important for your work in daily practice?	1: Very important – 5: not at all important.
8.	Do you agree with the message about this safety issue?	1: Yes, completely – 5: No, not at all.
9.	If not, can you indicate why you do not agree with the message about this safety issue?	Open question
10.	Are you of the opinion that one or more of your patients are at risk of the safety issue?	1: Yes, all patients who received Macugen (pegaptanib) 2: Yes, a specific group of patients who received Macugen (pegaptanib) 3: No, because I did not administer/provide Macugen (pegaptanib) 4: I don't know
Action taken		
11.	Did you search for more information regarding the safety issue?	Yes/No
12.	If so, did you visit the MEB website for more information regarding the safety issue?	Yes/No
13.	Did you discuss the safety issue with one or more of your colleagues?	Yes/No

Table 1. Continued

	Section/Question*	Answer categories
14.	Did you discuss the safety issue with (some of) your patients?	Yes/No
15a.	Did you advise one or more physicians to adjust treatment of one or more current patients? (hospital pharmacists only)	Yes/No
15b.	Did you change the treatment of one or more of your current patients? (ophthalmologists only)	Yes/No
16a.	If so, which adjustments have you advised? (hospital pharmacists only)	Open question
16b.	If so, in which way have you adjusted treatment? (ophthalmologists only)	Open question
17.	Did you take any other action in response to the safety issue?	No/Yes, namely …
Satisfaction with DHPC/e-mail		
18.	Does the DHPC offer you specific support for your work in daily practice?	Yes/No
19.	If not, do you have any suggestions for improvement?	Open question
20.	Does the e-mail offer you specific support for your work in daily practice?	Yes/No
21.	If not, do you have any suggestions for improvement?	Open question
22.	How satisfied are you in general with the provision of information by letter (DHPC)?	Visual analogue scale ranging from 1: very dissatisfied to 10: very satisfied.
23.	How satisfied are you with the provision of information by e-mail?	Visual analogue scale ranging from 1 very dissatisfied to 10: very satisfied.
24.	Do you think the link in the e-mail that provides access to the DHPC on the MEB website is useful?	1: Very useful – 5: not at all useful.
25.	In future, would you like to receive e-mails with similar information in addition to the letter (DHPC)?	1: Yes, for all drugs. 2: Yes, only for drugs that are relevant to my work in daily practice (for example not for specialized oncolytics). 3: No.
26.	Would you rather receive safety information via a letter, e-mail, or both?	1: Preferably via a letter (DHPC). 2: Preferably via an e-mail 3: Preferably via both.
27.	Would you rather receive such an e-mail from the pharmaceutical company, or the MEB?	1: Preferably from the pharmaceutical company. 2: Preferably from the MEB. 3: Preferably from both.
28.	Would you rather receive the letter (DHPC) from the pharmaceutical company, or the MEB?	1: Preferably from the pharmaceutical company. 2: Preferably from the MEB. 3: Preferably from both.
29.	Do you have any other suggestions for improvement of safety communication?	Open question

a Respondents were not presented all questions. For example: all questions regarding 'action taken in response to the DHPC' were automatically skipped in case a respondent indicated not to be aware of the safety issue and the recommendations that were given in the DHPC.
DHPC = Direct Healthcare Professional Communication; **MEB** = Dutch Medicines Evaluation Board.

To minimize the respondent burden, some questions were skipped automatically where appropriate (e.g. respondents who did not know what safety issue was identified were not asked if they took any consequent action). In addition, they were asked about their sex, age, whether they worked full time or part time, in a general or academic hospital, and how many years they had been professionally registered.

Results

Forty respondents (19%) completed the questionnaire (intervention group N=21; control group N=19; **Table 2; Figure 1**).

Table 2. Demographic characteristics respondents (N=40)

	Intervention group [N (%)] (N = 21)	Control group [N (%)] (N = 19)	Total [N (%)] (N = 40)	*P* Value
Response				
Before reminders	13 (12)	9 (9)	22 (10)	
Reminder 1	5 (5)	5 (5)	10 (5)	
Reminder 2	3 (3)	5 (5)	8 (4)	
Age [mean (range)]	51.1 (36-64)	52.6 (40-63)	51.8 (36-64)	p=0.668[a]
Sex				p=0.385[b]
Male	14 (67)	15 (79)	29 (73)	
Occupation				p=0.273[b]
Hospital pharmacist	9 (43)	5 (26)	14 (35)	
Ophthalmologist	12 (57)	14 (74)	26 (65)	
Employment				p=0.233[c]
Full time	18 (86)	19 (100)	37 (93)	
Hospital type				p=0.689[c]
General	18 (86)	15 (79)	33 (83)	
University	3 (14)	4 (21)	7 (18)	
Years of professional accreditation				p=0.108[c]
< 5 years	4 (19)	0 (0)	4 (10)	
5-10 years	0 (0)	0 (0)	0 (0)	
> 10 years	17 (81)	19 (100)	36 (90)	

a Mann Whitney U test; **b** χ^2; **c** Fishers' exact test. Differences in percentages may exist due to rounding.

An additional 14 healthcare professionals notified us that they would not fill out the questionnaire, 11 of whom did not administer or provide pegaptanib. The remaining three gave no reasons or gave other reasons for not participating. The majority of the respondents were male (73%), ophthalmologists (65%), working full time (93%), in a general hospital (83%). The mean age was 52 years (range 36–64 years), and most (90%) had been professionally registered for more than 10 years.

No significant differences were observed when comparing responders with non-responders with regard to sex, occupation and hospital type (χ^2, p=0.273; p=0.359; p=0.894, respectively). Respondents in the intervention group did not differ significantly

from those in the control group (**Table 2**). Eighteen intervention group respondents (86%) and thirteen control group respondents (68%) indicated that they had received the DHPC (FET p=0.265). In both groups, one respondent had not read the DHPC. Twelve respondents (67%) in the intervention group and ten (77%) in the control group reported that they had skimmed through the DHPC. The remaining respondents had read the DHPC carefully. Ten intervention group respondents (48%) indicated that they had received the initial e-mail, and four of them had read it carefully. The remaining six reported skimming through the e-mail.

Knowledge

Eighty-one percent of the respondents in the intervention group correctly identified the pegaptanib issue, versus 47 percent in the control group (FET p=0.046; **Figure 3a**). Over two thirds of both groups who were aware of the issue identified the correct recommendation (FET p=0.674; **Figure 3b**). Overall, 11 respondents were already aware of the issue before the DHPC was issued (no significant difference between groups; FET p=0.444), either from personal experience and/or common sense (N=6), from the scientific literature (N=2), from colleagues (N=2) or from an electronic newsletter (N=1) [**Table 3**]. Thirty percent of all respondents were of the opinion that generally it takes too much time to keep up with all new safety issues.

Attitudes

Almost all respondents (93%) considered drug safety information important or very important for their work in daily practice. Most intervention group respondents (72%) agreed with the warning. In the control group, 50 percent of the respondents agreed with the issue. All but one control group respondent indicated that their own patients were not at risk of the issue. Twenty-five of the 28 respondents who answered this question did not administer or provide pegaptanib (intervention group 94%; control group 80%).

Action Taken

Nine respondents (six ophthalmologists, three hospital pharmacists) in the intervention group versus none in the control group indicated that they had taken some form of action in response to the issue (FET p=0.01). The issue was mainly discussed with colleagues. One ophthalmologist mentioned that he had discussed with colleagues that close attention should be paid to the volume administered with intravitreal injections in general. Two respondents had searched for more information (both had visited the MEB website), one respondent had discussed it with a patient, and two ophthalmologists indicated that they had changed their patients' treatment.

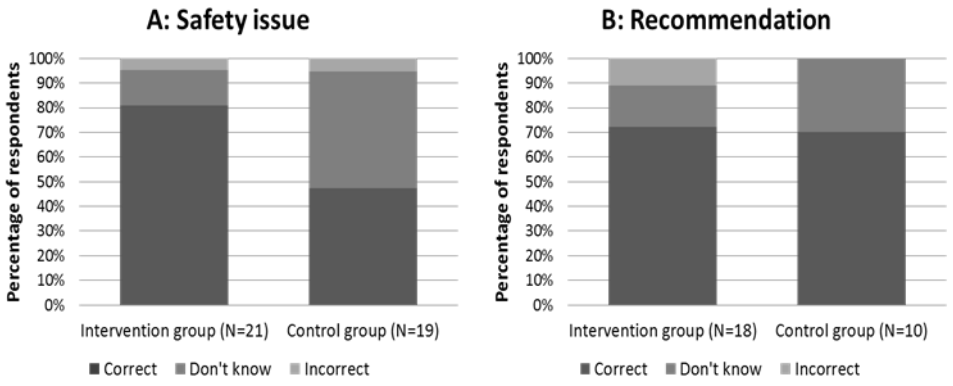

Figure 3
Healthcare professionals' knowledge **A** of the pegaptanib safety issue (Fisher's exact test, p=0.046); and **B** the corresponding recommendation (Fisher's exact test, p=0.674). The 'recommendation' question was not presented to respondents who had indicated that they did not know which safety issue had been identified for pegaptanib.

Table 3. Results of the questionnaire

	Intervention group		Control group	
	N[a]	n (%)	N[a]	n (%)
Knowledge				
Does it take you too much time to keep up with new drug safety issues? [yes(n)]	21	6 (29)	19	6 (32)
Can you specify which new safety issue was identified for Macugen (pegaptanib)? [correctly answered (n)]	21	17 (81)	19	9 (47)
Can you specify which recommendation was made in connection with this safety issue? [correctly answered (n)]	18	13 (72)	10	7 (70)
Were you aware of the Macugen (pegaptanib) safety issue before the DHPC and/or e-mail were sent? [yes (n)]	18	6 (33)	10	5 (50)
Attitude				
Do you think information about drug safety by means of DHPCs is important for your work in daily practice? [yes (n)]	21	19 (90)	19	18 (95)
Do you agree with the message about this safety issue? [yes (n)]	18	13 (72)	10	5 (50)
Are you of the opinion that one or more of your patients are at risk of the safety issue. [yes (n)]	18	0 (0)	10	1 (10)
Action taken				
Did you search for more information regarding the safety issue? [yes (n)]	18	2 (11)	10	0 (0)
If so, did you visit the MEB website for more information regarding the safety issue? [yes (n)]	16	2 (13)	10	0 (0)
Did you discuss the safety issue with one or more of your colleagues? [yes (n)]	18	8 (44)	10	0 (0)
Did you discuss the safety issue with (some of) your patients? [yes (n)]	18	1 (6)	10	0 (0)
Did you change the treatment of one or more of your current patients? (*ophthalmologists only*) [yes (n)]	10	2 (20)	9	0 (0)

Table 3. Continued

	N[a]	Intervention group n (%)	N[a]	Control group n (%)
Did you advise one or more physicians to adjust treatment of one or more current patients? (*hospital pharmacists only*) [yes (n)]	6	0 (0)	1	0 (0)
Did you take any other action in response to the safety issue? [yes (n)]	18	2 (11)	10	0 (0)
Satisfaction with DHPC/email				
Does the DHPC offer you specific support for your work in daily practice? [yes (n)]	17	13 (76)	12	6 (50)
Does the e-mail offer you specific support for your work in daily practice? [yes (n)]	9	7 (78)	NA	NA
How satisfied are you in general with the provision of information by letter (DHPC)? [on a visual analogue scale of 1-10 (mean (SD)]	21	7.1 (1.1)	19	5.0 (2.9)
How satisfied are you with the provision of information by e-mail? [on a visual analogue scale of 1-10 (mean (SD)]	10	7.2 (1.8)	NA	NA
Do you think the link in the e-mail that provides access to the DHPC on the MEB website is useful? [yes (n)]	10	6 (60)	NA	NA
In future, would you like to receive e-mails with similar information in addition to the letter (DHPC)? [yes (n)]	21	19 (90)	19	18 (95)
Would you rather receive safety information via a letter, e-mail, or both?	19		18	
- DHPC		3 (16)		2 (11)
- E-mail		10 (53)		10 (56)
- Both		6 (32)		6 (33)
Would you rather receive such an e-mail from the pharmaceutical company, or the MEB?	16		16	
- Pharmaceutical company		0 (0)		0 (0)
- MEB		12 (75)		11 (69)
- Both		4 (25)		5 (31)
Would you rather receive the letter (DHPC) from the pharmaceutical company, or the MEB?	11		9	
- Pharmaceutical company		1 (9)		1 (11)
- MEB		7 (64)		5 (56)
- Both		3 (27)		3 (33)

a N represents the number of respondents that answered a particular question. The total number of respondents per question can differ, depending on previous answers some subsequent questions were skipped in the online questionnaire. For example: all questions regarding 'action taken in response to the DHPC' were automatically skipped in case a respondent indicated not to be aware of the safety issue and the recommendations that were given in the DHPC. Differences in percentages may exist due to rounding.
DHPC = Direct Healthcare Professional Communication; **MEB**= Medicines Evaluation Board; **NA**= Not applicable.

One hospital pharmacist had recorded the issue in a computerized physician order entry system. Of note, the remaining ophthalmologist had reported the issue to the marketing authorization holder and the Dutch Pharmacovigilance Center.

Satisfaction with Risk Communication

The DHPC in general was rated with a mean score of 7.1 (standard deviation [SD] 1.1) out of 10 by the intervention group and 5.0 (SD 2.9) by the control group (Mann–Whitney U test p=0.024). The intervention group rated the e-mail with a score of 7.2 (SD 1.8). Fifty percent of the respondents in the control group and 76% of the intervention group thought that the traditional DHPC offered sufficient support for their work in daily practice (FET p=0.236). The intervention group valued the e-mail similarly to the DHPC, with 78 percent stating that the e-mail alone offered adequate support. The link to the DHPC as provided in the e-mail was rated useful by 60 percent of the intervention group respondents. Almost all respondents in both groups stated that they would like to receive an e-mail with safety information. Two thirds of them preferred to receive only e-mails about drugs that are relevant to their daily practice. Slightly more than half of the respondents who stated that they would like to receive an e-mail preferred not to receive the DHPC, and about a third preferred both. Thirteen percent indicated that they favoured the traditional DHPC despite wanting to receive the e-mail. The MEB was the preferred source of such information for both the DHPC as well as the e-mail (60 and 72%, respectively).

Discussion

Risk communication is increasingly receiving attention in pharmacovigilance, partly due to an increased call for transparency. The new European pharmacovigilance legislation has become operational, in which risk communication plays an important role, and in 2007 an EU DHPC template became available.[4,5,20] Despite these improvements, much can still be learned and optimized by addressing multiple factors. This study offers valuable information, as an additional e-mail may lead to better uptake of the information than only the DHPC. In general, uptake of a message is improved by repetition, especially when the message is similar but not identical.[13] This fits with the intervention group respondents being more knowledgeable about the pegaptanib issue and taking action more often than the control group respondents. The issue was mainly discussed with colleagues and appears to have been a reminder that pegaptanib should be administered carefully. In general, people want to make informed decisions about risks.[21] Two respondents searched for more information about the issue, underlining that additional information is desired and should be provided. Most respondents stated that they would like to receive an additional MEB e-mail in the future. This confirms that healthcare professionals have more trust in an objective information source, like the MEB, than in the pharmaceutical industry.[8,9,11] Successful risk communication largely depends on a

trustworthy information source and might be an important contribution to the impact of the intervention, as pharmaceutical companies are often distrusted.[8,22-24] When the trust and credibility of the source of the information are questioned, the message may not be heard, believed and acted upon.[22,25,26] Many factors play a role in constructing and deconstructing trust and, according to the so-called asymmetry principle, trust is lost more easily than it is rebuilt.[22]

The DHPC was rated higher by the intervention group than the control group. Thus, the e-mail may have influenced the intervention group's opinion about the DHPC. Repetition of a message does improve its uptake,[13] but it is unclear if satisfaction with the message is improved at the same time. Also, the link to the DHPC as provided in the e-mail may have improved its rating, as it was rated useful by 60 % of the respondents. The fact that they rated the DHPC similarly to the e-mail confirms that DHPCs remain an important communication tool.[8,10]

The question is raised as to when a DHPC can be considered sufficiently effective. Although the intervention group respondents were more knowledgeable and took action more frequently than the control group, not everyone in the intervention group could identify the correct recommendation. The challenge will be to develop evidence-based thresholds as to what knowledge and action levels are achievable and acceptable. Additional measures can be demanded whenever a threshold is not reached.

Strengths and Limitations

To our knowledge, this is the first randomized controlled study comparing the impact of an additional risk communication tool with that of the DHPC. Several national authorities provide an e-mail service informing subscribers of safety issues concerning drugs,[27-30] but their impact has not yet been assessed. These results therefore offer valuable insights to improve current risk communication.

This was a small study restricted to ophthalmologists and hospital pharmacists, and the response rate was fairly low despite two reminders, which limits its representativeness and generalizability. The low response rate may have caused bias, e.g. healthcare professionals who are unfamiliar with DHPCs or who are not specifically interested in drug safety issues may have been underrepresented. The control group consisted of slightly more ophthalmologists than the intervention group. Ophthalmologists could have had different opinions about the issue than the hospital pharmacists, but this was not the case (Mann–Whitney U test $p = 0.900$). Low response rates are not uncommon, especially in the case of online surveys.[31-33] In this case, it may have been attributable to the limited use of pegaptanib in the Netherlands[34] as shown by 11 healthcare professionals who indicated that they had not filled out the questionnaire

for that reason. Also, pegaptanib is a product with a very specific indication, and a highly educated group of prescribers (as was demonstrated by the 11 respondents) were already aware of the safety issue before the DHPC was issued. This might have been a reason for the non-responders to disregard the questionnaire. Yet no significant differences were observed between responders and non-responders. In view of its limitations, our study should be considered a starting point for future risk communication evaluations. Eleven intervention group respondents indicated that they had not received the pegaptanib e-mail, yet those respondents did fill out the questionnaire by using the link in the invitation e-mail that was sent to the same e-mail address and by the same sender. Those respondents might have overlooked the previous e-mail. The same issue holds for the DHPC, with nine respondents indicating that they had not received the DHPC. Previously, several physicians indicated that they often mistakenly throw away the DHPC together with direct mail advertising from pharmaceutical companies.[9] Also, electronic messages may be lost. A recall bias could be another possible explanation.

In order to minimize biased results, we did not perform an assessment before the DHPC was issued, nor did we provide detailed information about the study at the time of sending the e-mail, nor did we offer any incentives to increase response rates. Still, taking part in the study itself may have altered the attitude, knowledge and behaviour of the healthcare professionals. We are not able to verify to what extent this might have occurred.

Ultimately, measuring intended behaviour is just the start of evaluating the impact of risk communication, which should be supported by measurement of actual behaviour (removing the excess volume from the pre-filled pegaptanib syringe before administration) and the impact on clinical outcome, i.e. occurrence of the safety event (increased ocular pressure).[35]

Recommendations

Improving the impact of future risk communication, based on these results, will benefit public health and, ultimately, the patient. To this end, an additional e-mail sent by a national authority can be considered a promising additional tool. Healthcare professionals could be sent e-mails only about safety issues that are relevant to their specialization in order to prevent 'warning fatigue'. They should, however, still be given the opportunity to receive all e-mails, as was preferred by one third of the respondents in this study. Ideally, risk communication is a two-way process,[36,37] emphasizing the need for close involvement of healthcare professionals who are working in daily practice at the time when the DHPC is drafted. They know from experience what practising healthcare professionals already know about the drug and the safety issue. They are aware of the

concerns, needs and aspects that deserve to be emphasized in the DHPC.[38,39] With their input, the information can be tailored, e.g. by omitting information that is considered common knowledge, or by providing relevant background information.

Previous studies have shown that optimization of the format and content of DHPCs is possible[9,40,41] and that it can influence the impact of DHPCs.[42] A clear subject header on the e-mail or a notable symbol on the HPC's mailing envelope could make it stand out and prevent it from being discarded.[41,43] The content should be formulated to ensure that it is as readable and unambiguous as possible to make sure that it will be interpreted as intended and to avoid any confusion.[9,44,45] The most important aspects of the warning and clear recommendations should be mentioned first.[21] This is emphasized by the fact that a total of five respondents in our study who were aware of the pegaptanib issue could not correctly identify the recommendation, with two respondents in the intervention group incorrectly indicating that treatment with pegaptanib should be stopped.

Sending an additional e-mail is only one option. Other options, such as safety alerts in medical journals or computerized physician order entry systems, should also be explored, as these are also highly valued by healthcare professionals.[8] The impact of DHPCs may also be improved by taking the characteristics of the drug and the safety issue into account.[42]

Risk communication can be evaluated in different ways, including formative evaluation to assess the content of a message, process evaluation to determine whether the audience has received the message, and outcome evaluation to determine whether the intended effect of the message was achieved.[38] Each method has its methodological challenges, and studies should be carefully designed. When evaluating impact by means of surveys, low response rates should be anticipated, especially when the surveys are conducted online. Pilot tests should be carried out to provide a basis for thorough sample size calculations. Several respondents in our study indicated that they had not received the pegaptanib DHPC and/or e-mail. This should be investigated more thoroughly, as reaching the target audience is a prerequisite of effective risk communication. Since risk perception may differ between countries and there may be cultural differences regarding drug use,[46,47] it is necessary to compare the impact of DHPCs, as well as the experiences and preferences of healthcare professionals, with regard to DHPCs in different countries.

Conclusion

The results of this study indicate that an additional e-mail may strengthen the uptake of a written DHPC, as healthcare professionals' awareness of the safety issue was increased and more action was taken in response to the issue. This study may serve as a starting

point for new strategies to improve risk communication regarding safety issues associated with drugs and its impact on prescribing.

Acknowledgments

The authors thank the Dutch Pharmacist Association (KNMP) for providing the e-mail addresses of Dutch pharmacists. This study was supported by an unconditional grant from the Dutch Medicines Evaluation Board (MEB). The authors who are employed by the MEB (Pieter de Graeff, Sabine Straus, Peter Mol) state that the opinions in this paper are their own and do not necessarily reflect those of the MEB. None of the authors have any conflicts of interest that are directly relevant to the content of this article.

References

1 Piening S, Haaijer-Ruskamp FM, De Vries JTN, Van Der Elst ME, De Graeff PA, Straus SMJM, et al. Impact of safety-related regulatory action on clinical practice: a systematic review. Drug Saf 2012; 35(5):373-85.

2 Piening S, Reber KC, Wieringa JE, Straus SMJM, de Graeff PA, Haaijer-Ruskamp FM, et al. Impact of safety-related regulatory action on drug use in ambulatory care in the Netherlands. Clin Pharmacol Ther 2012; 04;91(5):838-45.

3 Dusetzina SB, Higashi AS, Dorsey ER, Conti R, Huskamp HA, Zhu S, et al. Impact of FDA drug risk communications on health care utilization and health behaviors: a systematic review. Med Care 2012;50(6):466-78.

4 The European Parliament and The European Council. DIRECTIVE 2010/84/EU. 2010; Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0074:0099:EN:PDF. Accessed 3 January, 2013.

5 The European Parliament and The European Council. REGULATION (EU) No 1235/2010. 2010; Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0001:0016:EN:PDF. Accessed 3 January 2013.

6 Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. Lancet 2003;362(9391):1225-30.

7 Lee LY, Kortepeter CM, Willy ME, Nourjah P. Drug-risk communication to pharmacists: assessing the impact of risk-minimization strategies on the practice of pharmacy. J Am Pharm Assoc 2008;48(4):494-500.

8 Piening S, Haaijer-Ruskamp FM, De Graeff PA, Straus SMJM, Mol PGM. Healthcare professionals self-reported experiences and preferences related to direct healthcare professional communications: a survey conducted in the Netherlands. Drug Saf 2012;35(11):1061-72.

9 Morrato EH, Curbow B, Crum RM, Nowels C, Feinleib M. Communicating drug risk to physicians: challenges and opportunities. Int J Risk Saf Med 2008;20(3):143-54.

10 Theophile H, Miremont-Salame G, Robinson P, Moore N, Begaud B, Haramburu F. Relevance of a "dear doctor letter" to alert healthcare providers to new recommendations for vitamin D administration. Eur J Clin Pharmacol 2011;67(7):681-6.

11 Medicines and Healthcare products Regulatory Agency / Ipsos Mori. Risks and benefits of medicines and medical devices - perceptions, communication and regulation. Report on quantitative research among health professionals. 2006. Available at: http://www.mhra.gov.uk/Publications/Corporate/Research/index.htm. Accessed 3 January, 2013.

12 Polimeni G, Russo A, Catania MA, Aiello A, Oteri A, Trifiro G, et al. Drug safety information through the internet: The experience of an Italian website. Drug Saf 2009;32(3):245-53.

13 McCullough JL, Ostrom TM. Repetition of highly similar messages and attitude change. J Appl Psychol 1974;59(3):395-7.

14 European Medicines Agency. Summary of Product Characteristics Macugen. 2012. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000620/WC500026214.pdf. Accessed 3 January, 2013.

15 European Medicines Agency. Opinions on safety variations. Adopted at the CHPM meeting of 16-19 July 2012. 2012. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/07/WC500130373.pdf. Accessed 3 January, 2013.
16 Dutch Medicines Evaluation Board. Belangrijke risico informatie: Risico op ernstige toename van de intraoculaire druk bij intravitreale injectie van de volume overmaat van het product Macugen (pegaptanib). 2012. Available at: http://www.cbg-meb.nl/NR/rdonlyres/E11AAE0D-0E90-4908-B321-8B139F2C6B45/0/MacugenDHPCNL13092012.pdf. Accessed 3 January, 2013.
17 Dutch Medicines Evaluation Board. Summary of Product Characteristics Macugen [in Dutch]. 2012. Available at: http://www.cbg-meb.nl/NR/rdonlyres/5FF14AE5-F1E6-4419-975A-98DF9949A8A5/0/MACUGENSmPCNL24Aug2012.pdf. Accessed 3 January, 2013.
18 Dutch Medicines Evaluation Board. Pictogram behorend bij DHPC Macugen. 2012. Available at: http://www.cbg-meb.nl/NR/rdonlyres/9EC641B9-F30B-4E67-BEBD-C3B638251D31/0/MacugenposterNL.pdf. Accessed 3 January, 2013.
19 Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud P-C, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. J Am Med Assoc 1999;282(15):1458-65.
20 European Commission. Volume 9A of the rules governing medicinal products in the European Union. Guidelines on Pharmacovigilance for medicinal products for human use. 2008. Available at: http://ec.europa.eu/health/files/eudralex/vol-9/pdf/vol9a_09-2008_en.pdf. Accessed 3 January, 2013.
21 Lundgren, R.E. & McMakin, A.H. Risk Communication. A handbook for communicating environmental, safety, and health risks. 3rd ed. Columbus: Battelle Press; 2004.
22 Slovic P. Perceived risk, trust, and democracy. Risk Anal 1993;13(6):675-82.
23 Berry DC. Risk, Communication and Health Psychology. 1st ed. Berkshire: Open University Press; 2004.
24 Lofstedt RE. The impact of the Cox-2 inhibitor issue on perceptions of the pharmaceutical industry: content analysis and communication implications. J Health Commun 2007;12(5):471-91.
25 Walaski P. Risk and Crisis Communications: methods and messages. Hoboken: Wiley; 2011.
26 McComas KA. Defining moments in risk communication research: 1996-2005. J Health Commun 2006;11(1):75-91.
27 U.S. Food and Drug Administration. Subscribe to MedWatch Safety Alerts. 2011. Available at: http://www.fda.gov/Safety/MedWatch/ucm228488.htm. Accessed 3 January, 2013.
28 Arzneimittelkommission der deutschen Ärzteschaft. Drug Safety Mail. Risikoinformationen aktuell per E-mail. 2011; Available at: http://www.akdae.de/Arzneimittelsicherheit/DSM/index.html. Accessed 3 January, 2013.
29 Australian Therapeutic Goods Administration. TGA Safety Information e-mail list. 2012. Available at: http://www.tga.gov.au/newsroom/subscribe-tga-safetyinfo.htm. Accessed 3 January, 2013.
30 Health Canada. Drugs and health products. Stay informed - MedEffect Canada. 2012. Available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/subscribe-abonnement/index-eng.php#subscribe. Accessed 3 January, 2013.
31 Sino CG, Munnik A, Schuurmans MJ. Knowledge and perspectives of Dutch home healthcare nurses regarding medication frequently used by older people. Int J Older People Nurs 2013;8(2):131-8.

32 Crouch S, Robinson P, Pitts M. A comparison of general practitioner response rates to electronic and postal surveys in the setting of the National STI Prevention Program. Aust N Z J Public Health 2011;35(2):187-9.

33 Suttle CM, Jalbert I, Alnahedh T. Examining the evidence base used by optometrists in Australia and New Zealand. Clin Exp Optom 2012;95(1):28-36.

34 Goossens L, Knoester P, Rutten-Van Molken M. Avastin (bevacizumab), Macugen (pegaptanib) and Lucentis (ranibizumab): Comparison of medication costs. Pharm Weekbl 2008;143(16):75-9.

35 Prieto L, Spooner A, Hidalgo-Simon A, Rubino A, Kurz X, Arlett P. Evaluation of the effectiveness of risk minimization measures. Pharmacoepidemiol Drug Saf 2012;21(8):896-9.

36 Slovic P, Peters E, Grana J, Berger S, Dieck GS. Risk perception of prescription drugs: results of a national survey. Drug Inf J 2007;41(1):81-100.

37 Edwards B, Chakraborty S. Risk communication and the pharmaceutical industry: what is the reality? Drug Saf 2012;35(11):1027-40.

38 Fischhoff B, Brewer NT, Downs JS. Communicating risks and benefits. An evidence-based user's guide. 2011. Available at: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM268069.pdf. Accessed 15 February 2013.

39 Fischhoff B. Why (cancer) risk communication can be hard. J Natl Cancer Inst Monographs 1999;25:7-13.

40 Weatherby LB, Nordstrom BL, Fife D, Walker AM. The impact of wording in "dear doctor" letters and in black box labels. Clin Pharmacol Ther 2002;72(6):735-42.

41 Mazor KM, Andrade SE, Auger J, Fish L, Gurwitz JH. Communicating safety information to physicians: an examination of dear doctor letters. Pharmacoepidemiol Drug Saf 2005;14(12):869-75.

42 Reber KC, Piening S, Wieringa JE, Straus SMJM, Raine JM, De Graeff PA, et al. When Direct Healthcare Professional Communications have an impact on inappropriate and unsafe use of medicines. A retrospective analysis of determinants of impact of safety warnings. Clin Phar Ther 2013;93(4):360-5.

43 Kasperson RE, Renn O, Slovic P, Brown HS, Emel J, Goble R, et al. The social amplification of risk: a conceptual framework. Risk Anal 1988;8(2):177-87.

44 Fischhoff B. Risk perception and communication unplugged - 20 years of process. Risk Analysis 1995;15(2):137-45.

45 Bahri P. Public pharmacovigilance communication: a process calling for evidence-based, objective-driven strategies. Drug Saf 2010;33(12):1065-79.

46 Deschepper R, Grigoryan L, Lundborg CS, Hofstede G, Cohen J, Kelen GVD, et al. Are cultural dimensions relevant for explaining cross-national differences in antibiotic use in Europe? BMC Health Serv Res 2008;8:123.

47 Grigoryan L, Burgerhof JGM, Degener JE, Deschepper R, Lundborg CS, Monnet DL, et al. Attitudes, beliefs and knowledge concerning antibiotic use and self-medication: a comparative European study. Pharmacoepidemiol Drug Saf 2007;16(11):1234-43.

Chapter 7

Summary & General Discussion

This thesis focuses on the impact of risk communication of safety issues of drugs. Throughout a drugs' post marketing lifecycle serious safety issues may emerge,[1-3] which can lead to hospitalization, disability, or even death of patients.[4,5] These issues need to be communicated to healthcare professionals. In Europe, this is mainly done with paper based Direct Healthcare Professional Communications (DHPCs). These warning letters are sent by the responsible pharmaceutical company at the instigation of national and/or the European Medicines Agency (EMA) and are aimed at ensuring safe and effective use of medicinal products.[6] However, DHPCs have not always been successful in effectively communicating the intended information to the healthcare professionals.[7-9] In some cases, drugs had to be taken off the market, because warnings were not sufficiently complied with. The new pharmacovigilance legislation that came into force in July 2012, stipulates that the outcome of risk minimization measures should be measured.[10,11] A reference framework regarding the effects of drug safety warnings on clinical practice is needed and could be obtained by identifying the effect of previous risk minimisation measures.[12] However, a comprehensive overview that could contribute to the debate about the effectiveness of DHPCs was lacking, and experiences and preferences of Dutch healthcare professionals with regard to DHPCs were unknown.

Therefore, the main objectives of the Communicating Risk Effectively (CORE) project were:

- To provide an overview of the impact of DHPCs and to explore different determinants of variation in impact. (Part 1, Chapters 2, 3, 4)
- To explore the experiences and preferences of Dutch healthcare professionals with regard to the DHPC and to determine the added value of a new risk communication method, based on these preferences. (Part 2, Chapters 5, 6)

In this chapter we discuss the main findings of the CORE project, the methodological considerations, and the implications of this research for current practice, as well as for future research.

Main findings

Part 1 - The impact of safety-related regulatory action

In **chapter 2**, the results are given of the systematic literature search that we conducted using the online literature databases Medline and Embase. We provided an overview of studies that assessed the impact of DHPCs, Black Box warnings, and Public Health Advisories. The search resulted in 52 relevant articles. We found that the evidence is primarily based on two drug groups, namely the third-generation oral contraceptives

(increased risk of thrombosis) and selective serotonin reuptake inhibitors (risk of suicide in adolescents and children) and one drug, namely cisapride (risk of serious cardiac arrhythmias). The remaining articles described a broad variety of drugs and drug groups. Almost half of the studies had inadequate before/after designs and heterogeneity in analyses and outcome measures hampered the reporting of overall effect sizes. Studies with adequate interrupted time series design reported a more mixed impact of safety warnings than before/after studies. When unintended effects were assessed in case of selective serotonin reuptake inhibitors (suicides, spillover effects to non-targeted population) and third-generation oral contraceptives (conceptions, abortions), these were almost always present, showing the relevance of considering not only the intended but also the unintended effects of safety warnings. Furthermore, we concluded that safety-related regulatory action can have some impact on clinical practice but firm conclusions are difficult to draw. These results showed that there is a clear need for further research with appropriate study designs, and statistical analyses to understand the impact of safety-related regulatory action.

The impact of a large group of Dutch DHPCs on drug use was evaluated in **chapter 3**. Nationwide dispensing data for the period 2000–2008 for new users of drugs with one or more DHPCs were assessed. Fifty nine DHPCs were included for 46 drugs or drug groups. Impact on short-term volume of use was evaluated with regression models, and the presence of long-term changes in use with interrupted time series analyses incorporating pre-existing trends. We found that in the short term, almost half of all drugs with a DHPC showed a decrease in use in the year after the DHPC was issued compared with the year before. Long term changes in use were observed for a third of the drugs with a DHPC, resulting in a mean decrease in drug use of 27%, ranging from -10% to -67%. Changes in use were not clearly related to pre-existent trends in use.

Based on these results we concluded that once safety issues for drugs were identified that warranted strong regulatory action, namely DHPCs, these resulted in short term reductions in use for almost half of the cases and substantial long term reductions in use of a third of the cases. Potential determinants for the impact on prescribing could be the type of adverse drug event, availability of alternative agents, the type of prescriber, the seriousness of the safety issue, and the medical need for the drug.

To study this further we explored which characteristics determine impact of Dutch DHPCs in **chapter 4**. We included the same 59 DHPCs that were issued for 46 drugs between 2001 and 2008 for ambulatory care drugs. Using multiple linear regression we examined the impact on the relative change in new drug use post DHPC of: the time to DHPC from the registration date of the drug, the trend in use in the 12 months before the

DHPC was issued, the degree of therapeutic innovation of the drug, whether the drug was initially prescribed by a specialist or not, whether it was a first or a repeated DHPC, availability of a DHPC template when the DHPC was issued, and the type of serious safety issue. We observed that DHPCs had less impact on use of specialist drugs than non-specialist drugs. DHPCs that were issued after a template was made available that emphasized the safety issue contributed to a lower drug use. Irreversible, potentially catastrophic safety issues,[13] namely with a risk of death and disability were associated with lower use. A marginally significant effect was found for drugs with a decreasing trend in use before the DHPC was issued. No significant impact was observed for the degree of therapeutic innovation, repeated DHPCs, and serious safety issues with a risk of hospitalization. These determinants together explained 39% of the overall variation in change of new drug use and should be considered as a first exploration of determinants that influence the impact of DHPCs.

We concluded that risk communication of safety issues of drugs can be effective, specifically in case of well-structured information, and very serious safety issues. Effectiveness may be improved by tailoring DHPCs and adding other communication channels, for example for drugs that are increasingly being used after a DHPC is issued.

Part 2 - Towards optimisation of the impact of safety-related regulatory action; a focus on Direct Healthcare Professional Communications.

In **chapter 5**, we developed and pilot tested a questionnaire to assess experiences and preferences of Dutch healthcare professionals with DHPCs. The questionnaire and two reminders were sent to a random sample of approximately 3.500 GPs, internists, community- and hospital pharmacists in the Netherlands. A third of the healthcare professionals returned the questionnaire. Although the majority of the healthcare professionals considered risk information of medicinal products to be important, a substantial group was not familiar with the DHPC as a tool for risk information. Pharmacists appeared to be more aware of, and more responsive to, safety issues than physicians. The respondents indicated mainly other channels as the source for their knowledge of some recent drug safety issues. Our study also showed that the healthcare professionals had more trust in safety information provided by the Dutch Medicines Evaluation Board (MEB) than by the pharmaceutical industry. The respondents preferred safety information to be issued by an independent source, such as the MEB, or their own professional associations. The preferred alternative channels of drug safety information were e-mail, medical journals, and computerized physician order entry systems.
We concluded that safety information of drugs does not always reach healthcare professionals through DHPCs and that special effort is needed to reach general

practitioners. We recommended that alternative and/or additional methods of risk communication are developed using electronic methods and medical journals. Moreover, (additional) risk communication coming from an independent source like the MEB should be considered.

In **chapter 6**, we showed the results of a pilot study that was set up to evaluate the value of an e-mail which was sent to healthcare professionals in addition to a DHPC for the drug pegaptanib. We conducted a randomized controlled trial in which the intervention group received both the pegaptanib DHPC, as well as the MEB e-mail and the control group received the traditional paper based DHPC only. Two weeks later the study population received an invitation to fill out an online questionnaire. Questions were asked about the respondents' knowledge and perception of the pegaptanib issue, and any action they had taken in response to the issue. Additional questions were asked about their satisfaction with the DHPC and the e-mail. Forty respondents completed the questionnaire. Respondents who received the additional e-mail were more knowledgeable about the pegaptanib safety issue and took action more often than the respondents who received the paper based DHPC only. The issue was discussed with colleagues by most respondents. The majority of both the intervention group and the control group indicated that they would like to receive an e-mail with safety information about drugs in the future. The MEB was the preferred source of information for the DHPC as well as the e-mail.
We concluded that issuing an additional e-mail resulted in a better uptake of safety information than a written DHPC only, as respondent's awareness of the safety issue was increased and more action taken in response to the issue.

Methodological considerations

New drug use as an outcome measure to assess the impact of DHPCs

In **chapter 3** and in **chapter 4**, we focused on new drug use as an outcome measure to assess the impact of DHPCs. It should be noted, that a decrease in use is not always the intended impact of a DHPC.[14-16] The impact of DHPCs can - and should - also be analysed using outcome measures that are directly attuned to the safety issue, as indicated in **chapter 1**. Such outcome measures are, for example, concomitant use of contraindicated drugs[17] or how often healthcare professionals order recommended laboratory tests to identify early potential drug toxicity.[18] The results of this study can only be used to anticipate the impact of DHPCs on new drug use and any additional action that is based on these results should be carefully considered. Nevertheless, we think that new drug use was an appropriate outcome measure to explore the role of determinants of impact of

DHPCs, since it is an outcome measure that can reliably be assessed for a large group of drugs. Also, new drug use is a more sensitive measure than overall use, since changes in prescribing behaviour can more likely be expected in new users.[19] Incorporating a classification of the hoped for and expected outcome of the DHPCs in order to analyse its impact on a more specific outcome measure would only have been possible if it would have been made in a prospective setting, at the time a DHPC is issued. These studies can be considered a starting point for future studies that will assess more specific outcome measures that are attuned to the recommendations in the DHPC.

Limited number of determinants

In **chapter 4** we included a set of seven determinants to assess which characteristics determine the impact of Dutch DHPCs. We limited the range of determinants due to the sample size and its corresponding power. Our full model explained 39% of the overall variation in DHPC effect size. Other factors were not included in our model that might also have attributed to variations in the impact of DHPCs, for example media attention, the incidence of safety issues, safety issues related to off-label use, and availability of alternative treatment. It has been suggested that media attention can play an important role in the impact of DHPCs as they can amplified the risks.[20-22] We performed an explorative lay- and professional literature search for a selection of the DHPCs in our study which resulted in too little information to include presence of media attention in our model. Likewise, the incidence of the safety issue at hand could not be included, since this aspect was not mentioned in the majority of the DHPCs. DHPCs concerning safety issues related to 'off label' use were too few in number, which led to insufficient variation within the variable for incorporation into our model. Alternative treatment was available for almost all drugs and was indirectly covered by the innovation variable. More innovative drugs did not show greater impact of a DHPC on drug use that less innovative drugs. Therefore, it seems unlikely that availability of an alternative treatment would be a major determinant. This issue could be addressed by repeating this study in a few years, when more DHPCs have been issued making it possible to include more determinants in a similar model. For now, our study should be considered as a first exploration of determinants that influence the impact of DHPCs that warrant further confirmation and extension.

Generalizability

In the studies in **chapter 3** and **chapter 4** a large number of DHPCs was included that were issued over a period of eight years. The DHPCs covered a wide variety of safety issues and drugs representing all main therapeutic classes prescribed in ambulatory care. Using the

same method to assess the impact of DHPCs enables the comparison of the effects of the different DHPCs and increases the generalizability of the results.

The fairly low response rates of the studies in **chapter 5** and **chapter 6** limit the generalizability of the results. Despite sending two reminders in both studies, only 34% and 19%, respectively, of the healthcare professionals responded. Low response rates in surveys amongst healthcare professionals are not uncommon due to e.g. increasing workloads, survey fatigue and a low priority of completing questionnaires especially among physicians.[23-29] Still, the low response may have biased our results in that healthcare professionals who are unaware of, or not interested in, DHPCs could be underrepresented in our samples. This could mean that, in daily practice, even fewer healthcare professionals are aware of DHPCs and specific safety issues than observed in our study, underlining the need for improvements in current risk communication. Johnson and Wislar stated that the response rate might not be as strongly associated with the quality and representativeness of a survey and stressed the importance of selecting a representative sample of the population.[29] In **chapter 5**, we were unable to analyse any characteristic of the non-responders due to the anonymous nature of the questionnaire. We could only report that our sample was representative for the Dutch setting in terms of sex,[30] and the percentage of GPs who work part-time.[31] We found no significant differences between early and late responders, except for two variables; it is possible that the non-responders had different preferences with regard to the pharmacists and pharmacotherapy meetings than the responders. Apart from these two variables, the results of this study were, in all likelihood, not affected by non-response bias. When comparing the responders to the non-responders in **chapter 6** with regard to their sex, occupation and hospital type no significant differences were observed. The low response in this study could be attributed to the limited use of pegaptanib in the Netherlands.[31] Eleven healthcare professionals responded to our survey invitation by stating that they would not fill out the questionnaire because they did not administer or provide pegaptanib. Twenty-five respondents who did fill out the questionnaire indicated the same. This emphasizes the importance of a pilot study to provide a basis for thorough sample size calculations in case a survey is the preferred study design.

It is not clear to what extent the results of our studies can be generalized to other countries. We evaluated the impact of Dutch DHPCs and the experiences of Dutch healthcare professionals. Often the same DHPCs, albeit translated, are issued throughout Europe, especially for drugs that are registered at a European level. However, healthcare professionals in diverse countries may respond differently to the DHPCs. Risk perception may differ and cultural differences regarding drug use can exist.[33,34] For example, trust in institutions, one of the risk perception factors that determine how a risk is perceived can

be expected to vary between countries as the interpretation of benefits and risks of drugs has shown to vary between national agencies.[35,36] A message will not be heard, believed and acted upon when trust and credibility of the source of the information are questioned.[37] This means that healthcare professionals in certain other countries might not prefer to receive drug safety information from their national drug regulating authority. This would underline that each situation needs to be assessed individually. An EU wide study would allow for a comparison of the (determinants of) impact of DHPCs as well as the experiences and preferences of healthcare professionals with regard to DHPCs in different countries. This will provide much needed information regarding the necessity of nationally tailored risk communication strategies.

Future research

Assessment of impact of safety-related regulatory action

The results of our systematic review indicate a clear need for further research in order to fully understand the impact of safety-related regulatory action. The impact of DHPCs should not only be analysed by assessing drug use. Outcome measures that are directly attuned to the safety issue should also be assessed. Clusters of DHPCs with the same recommendation could be analysed to get more insight into how the impact of DHPCs on more specific outcomes can best be anticipated. This can be facilitated by prospectively classifying the recommendations that are made in the DHPCs at the time they are issued.

Several other factors that might also attribute to variations in the impact of DHPCs were not included in the model in **chapter 4**. By repeating this study in a few years, when more DHPCs have been issued, and the content of the DHPCs is possibly even further optimized, the issue of the limited sample size could be solved and more factors could be included in the model.

Both the intended and the anticipated unintended effects of safety warnings should be assessed. Interrupted time series would be the preferred design as it allows for greater reliability in assessing the impact of safety warnings in comparison to before/after designs. Also, all individual warnings that are issued for the drug in question should be assessed instead of only a selection and the impact should be reported per warning instead of an overall effect. This way it will be possible to gain more knowledge about the specific type of warning that is most effective in changing behaviour of physicians.

Optimisation of the impact of safety-related regulatory action

Within the field of environmental risk communication a great deal of research has already been performed that can be used for improving communication of drug safety issues.[38-40]

In our studies we focused on getting empirical evidence for a few but important aspects of risk communication. These findings add to the practical approaches described in a specific US-based practical guide on how to plan, implement, and evaluate health communication programs.[41] With regard to surveys, low response rates should be anticipated, especially when the survey is conducted online. Pilot tests should be carried out to provide a basis for thorough sample size calculations.

The respondents of our survey in **chapter 5** indicated they would like to receive information of safety issues of drugs via e-mail from the MEB, which we put to the test in a randomized clinical trial in **chapter 6**. Similar randomized clinical trials could be set up to assess the impact of a safety warning that are communicated by other highly valued communication sources or channels. These channels need to be chosen based on the goal of risk communication, i.e. sharing new information, changing beliefs of drug benefits and risks, or changing healthcare professional behaviour. Particularly in the latter case more interventions may be needed to achieve long-term changes in behaviour.

From the studies described in **chapter 4**, **chapter 5**, and **chapter 6**, we know that context matters. Several risk perception factors (irreversibility, high catastrophic potential and trust in institutions) play a role in the way safety issues of drugs and associated risk communication are perceived by healthcare professionals. Since not all risk perception factors were included in these studies, the influence of other factors, like uncertainty, understanding, and the ethical/moral nature is not known. Unfortunately, most risk perception research has been performed amongst the lay public, mostly regarding risks other than serious safety issues of drugs. Future research could provide more insight, for example by studying how physicians weigh benefits and risks when prescribing drugs for which a DHPC was issued. The lay public rates the benefits and risks of several drugs differently.[21] It is to be expected that the same holds for physicians. In general, people are willing to accept higher risks in case of more benefits.[21] The fact that physicians are making risk related decisions for their patients, instead of themselves should be taken into account. For it has been shown that physicians would choose riskier treatment options for themselves than for their patients.[42] On the other hand, one study suggests that regulators, physicians and patients may weigh new serious drug risks similarly, when presented in the context of other benefits and risks of an oral anti-diabetes drug. An increased, but in absolute terms still small risk of bladder cancer of a hypothetical oral anti-diabetes drug did not affect drug choice of all three stakeholder groups.[43] Risk communication tools, e.g. decision aids to facilitate shared decision making, may be explored when differences in benefit/risk perceptions are anticipated.
Better understanding of the role risk perception factors play could provide guidance for the optimization of the impact of future DHPCs.[44] This will help policy to improve risk

communication methods, anticipate unintended effects, and develop new risk management strategies.[45] The impact of DHPCs issued for safety issues other than administration issues and for drugs that are more widely used should also be assessed. Specific attention should be paid to DHPCs communicating newly identified safety issues, as this new information might conflict with the views that healthcare professionals have of these drugs. According to the theory of cognitive dissonance, this could cause them to disregard the new information.[45,46]

Implications for regulatory policy and practice

Risk communication is receiving more and more attention within the field of pharmacovigilance, partly due to an increased call for transparency. In 2007 a DHPC template became available and in 2012 the new pharmacovigilance legislation became operational in which risk communication plays an important role.[6,10,11] Despite these improvements, still a lot can be learned and optimized. Based on this thesis, the following recommendations can be given (**Table 1**). Risk communication of safety issues of drugs should be improved by addressing multiple factors.

Table 1. Main recommendations

1.	**Improve communication methods**
	Communicate safety issues of drugs through an independent, trustworthy source.
	Use new channels, e.g. e-mail, to communicate safety issues.
	Make the DHPC stand out to healthcare professionals, e.g. with a picture of a yellow hand on the envelope.
2.	**Increase involvement of healthcare professionals**
	Involve healthcare professionals in the DHPC drafting process.
	Improve healthcare professionals' awareness of authorities.
	Educate healthcare professionals about risk communication of safety issues of drugs.
3.	**Improve evaluation of impact**
	Define and classify the intended effects of DHPCs prospectively.
	Determine appropriate outcome measures to assess the impact of DHPCs.
	Determine thresholds for when DHPC can be considered effective.
	Anticipate unintended effects of DHPCs.

1. Improve communication methods

Trust plays an important role in the risk communication process and pharmaceutical companies are often distrusted.[47,48] A complex set of factors plays a role in the construction and deconstruction of trust and unfortunately, it is easier to loose than to generate or rebuild trust which was outlined by the so-

called 'asymmetry principle'.[35] Hence, we recommend that drug safety issues should be communicated by a trustworthy source like the MEB.[49,50]

New channels like e-mail could be used to communicate safety issues of drugs. Healthcare professionals should be able to indicate if they want to receive such an e-mail about all drugs or a selection only. This will prevent occurrence of a so-called 'warning fatigue' due to an overload of information.

In this thesis, we did not study if, and in what way the content of the DHPC could be improved. Even though the impact of the DHPC on drug use was increased after the DHPC template became available, further optimization of the format and content of the DHPC is possible. Use of symbols is essential to make the DHPC stand out to healthcare professionals.[49,50] It is recommended that the letter should be sent with an extra symbol such as a picture of an orange hand printed on the envelope as is currently done in the Netherlands in cases that require immediate action from the healthcare professional. A different colour, e.g. yellow, could be used to distinguish DHPCs to merely alert healthcare professionals of a drug safety issue from cases where immediate action is required. On the envelope of the DHPC and in the header of an email the drug and the safety issue should ideally be mentioned.

The most important information is not always presented adequately in the DHPC and readability and clarity can be insufficient.[50] The way the numbers are presented and risks are framed has a major influence, as for example the 'Pill scare' has shown.[21,41,51,52] Framing of risks (e.g. indicating how many patients have died versus how many patients survived the adverse drug event) seems to influence lay people and healthcare professionals similarly.[21] To establish the optimal presentation of risks in DHPCs previous research among lay people can be studied. However, healthcare professionals do not always have the same needs regarding risk information as lay people.[41] When communicating to healthcare professionals, more sophisticated language can be used, and references can be given to scientific background information.[53] Nevertheless, a so-called polysemic message, which is a message that can be interpreted in several ways should be avoided as it could create confusion amongst the target audience. The content of the DHPC, especially the recommendations, should be formulated as unambiguous as possible.[51,54,55] The most important aspects of the safety issue, including the recommendations, should be mentioned first.[53] To avoid unintended effects that could be caused by a polysemic message, the content of the DHPC should be pre-tested by the target audience.[53]

2. Increase involvement of healthcare professionals

Successful risk communication does not only depend on optimal communication methods, but also on engagement of the receiver. Ideally, risk communication is a two way process emphasizing the need for close involvement in the DHPC drafting process of healthcare professionals who are working in daily practice.[38,39,45,52,56,57] Also, professional associations could be involved in drafting and informing their members of DHPCs, since they are highly valued and considered to be credible information sources.[52,54] It is known how difficult it is to predict what risks are relevant to others.[41] Provided the correct specific healthcare professional is involved one may assume that they know from experience what is already known about the drug and the safety issue and what not. They are aware of what the concerns and needs are and which aspects deserve to be emphasized in the DHPC.[41,52] This approach could potentially avoid unintended effects that occurred with the SSRIs and situations like the pill scare could possibly be contained.[51]

A possible approach could be the Mental Models method.[52] By interviewing healthcare professionals as well as regulators, their opinions can be identified and any differences can be addressed. This approach is quite time consuming however, and might be more useful as a preparation to improve the format and content of DHPCs in general.[53] It would be less suitable during a crisis situation for valuable time might be lost. Furthermore, validated tests are available that can be used to test the readability of DHPCs in terms of sentence construction, length and type of words used.[41]

Healthcare professionals see a distinct role for regulatory authorities in communicating safety issues and their visibility amongst healthcare professionals should be improved. To assist healthcare professionals in their responsibility to keep abreast of newly identified safety issues of drugs, they should be educated that at some points in their career they will be subject to risk communication, for example during their training. This could be integrated with education on how to report safety issues.

3. Improve evaluation of impact

Risk communication can be evaluated in different ways. With formative evaluation the content of the message can be assessed, process evaluation can for instance be used to determine whether the audience has received the message and with outcome evaluation it can be determined whether the intended effect of the message was achieved.[41]

The intended effects of DHPCs should be defined and classified prospectively in order to be able to assess their effectiveness using the most appropriate outcome measure. These outcome measures should preferably be attuned to the safety issue, for example, concomitant use of contraindicated drugs[17] or how often health-care professionals order recommended laboratory tests to identify early potential drug toxicity.[18] Subsequently, it is important to determine at which point a DHPC can be considered sufficiently effective. Stating that the impact of risk minimization measures should be evaluated is useful only when thresholds are set and additional action is demanded whenever such a threshold has not been reached.[58-60] This will not be easy in view of the current lack of information about the effectiveness of these measures. For example it is not known whether a 'ceiling effect' could occur that will hinder a DHPC and additional risk communication methods to be any more effective. Moreover, there are no 'universally acceptable risks', as it depends on the context whether the achieved risk reduction is sufficient.[61] In the case of the DHPCs it means that not all adverse drug events can be prevented, despite taking into account all precautions.[62] Also, the ease with which thresholds can be set depends on the type of outcome measure. They can be determined fairly easy for the number of drug prescriptions, or laboratory tests. But how many adverse events can be accepted, would be more difficult keeping in mind underreporting and their possible similarity with a symptom of the disease in question. The challenge in the near future will be to generate evidence that can be used to establish what is achievable and what is not. For each DHPC the potential unintended effects should be verified and monitored. By anticipating the unintended effects, for example by giving additional information, problems that have occurred with selective serotonin reuptake inhibitors (decreased use by non-targeted population) and the third generation contraceptives (increased number of abortions)l can be avoided in the future.

Final conclusion

This thesis gives an overview of the impact of DHPCs and its determinants. Although long term decreases in use were observed after only a third of the DHPCs, the decrease was substantial. DHPCs were specifically effective in case of well-structured information, and very serious safety issues. Dutch healthcare professionals preferred to receive safety information through electronic methods and from an independent source. An additional e-mail that was sent by the Dutch Medicines Evaluation Board strengthened the effect of a written DHPC as healthcare professionals' awareness of the safety issue was increased

and more action was taken in response to the issue. Currently, the DHPC has a clear added value. Any future developments will have to be monitored. From an unimpeded, research point of view, recommendations were given that can be used to improve current risk communication of safety issues of drugs. Regulatory decisions are affected by governance of the health sector, which may complicate implementation. A flexible attitude is required of all stakeholders to improve safe use of drugs which will benefit public health and, ultimately, the patient.

References

1 Mol PGM, Straus SMJM, Piening S, De Vries JTN, De Graeff PA, Haaijer-Ruskamp FM. A decade of safety-related regulatory action in the Netherlands: A retrospective analysis of direct healthcare professional communications from 1999 to 2009. Drug Saf 2010 33(6):463-474.

2 Giezen TJ, Mantel-Teeuwisse AK, Straus SMJM, Schellekens H, Leufkens HGM, Egberts ACG. Safety-related regulatory actions for biologicals approved in the United States and the European Union. J Am Med Assoc 2008 10;300(16):1887-1896.

3 Lasser KE, Allen PD, Woolhandler SJ, Himmelstein DU, Wolfe SM, Bor DH. Timing of new black box warnings and withdrawals for prescription medications. J Am Med Assoc 2002 05;287(17):2215-2220.

4 Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: Prospective analysis of 18 820 patients. Br Med J 2004 07;329(7456):15-19.

5 Sari AB-, Sheldon TA, Cracknell A, Turnbull A, Dobson Y, Grant C, et al. Extent, nature and consequences of adverse events: Results of a retrospective casenote review in a large NHS hospital. Qual Saf Health Care 2007 16(6):434-439.

6 European Commission. Volume 9A of the rules governing medicinal products in the European Union. Guidelines on Pharmacovigilance for medicinal products for human use. 2008; Available at: http://ec.europa.eu/health/files/eudralex/vol-9/pdf/vol9a_09-2008_en.pdf. Accessed 24 January, 2013.

7 Goldman SA. Communication of medical product risk: How effective is effective enough? Drug Saf 2004 27(8):519-534.

8 Woosley RL. Drug labeling revisions - Guaranteed to fail? J Am Med Assoc 2000 12;284(23):3047-3049.

9 Dusetzina SB, Higashi AS, Dorsey ER, Conti R, Huskamp HA, Zhu S, et al. Impact of FDA drug risk communications on health care utilization and health behaviors: A systematic review. Med Care 2012 50(6):466-478.

10 The European Parliament and The European Council. DIRECTIVE 2010/84/EU. 2010; Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0074:0099:EN:PDF. Accessed 24 January, 2013.

11 The European Parliament and The European Council. REGULATION (EU) No 1235/2010. 2010; Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0001:0016:EN:PDF. Accessed 24 January, 2013.

12 European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Module XV - Safety communication. 2012; Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500130396.pdf. Accessed 24 January, 2013.

13 Covello VT, Peters RG, Wojtecki JG, Hyde RC. Risk communication, the West Nile virus epidemic, and bioterrorism: Responding to the communication challenges posed by the intentional or unintentional release of a pathogen in an urban setting. Urban Health 2001 78(2):382-391.

14 Olfson M, Marcus SC, Druss BG. Effects of food and drug administration warnings on antidepressant use in a national sample. Arch Gen Psychiatry 2008 65(1):94-101.

15 Valuck RJ, Libby AM, Orton HD, Morrato EH, Allen R, Baldessarini RJ. Spillover effects on treatment of adult depression in primary care after FDA advisory on risk of pediatric suicidally with SSRIs. Am J Psychiatry 2007 164(8):1198-1205.
16 Williams D, Kelly A, Carvalho M, Feely J. Effect of the British warning on contraceptive use in the General Medical Service in Ireland. Ir Med J 1998 91(6):202-203.
17 Starner CI, Schafer JA, Heaton AH, Gleason PP. Rosiglitazone and pioglitazone utilization from January 2007 through May 2008 associated with five risk-warning events. J Managed Care Pharm 2008 14(6):523-531.
18 Willy ME, Manda B, Shatin D, Drinkard CR, Graham DJ. A Study of Compliance with FDA Recommendations for Pemoline (Cylert(registered trademark)). J Am Acad Child Adolesc Psychiatry 2002 41(7):785-790.
19 Wilkinson JJ, Force RW, Cady PS. Impact of safety warnings on drug utilization: Marketplace life span of cisapride and troglitazone. Pharmacotherapy 2004 24(8):978-986.
20 Martin RM, May M, Gunnell D. Did intense adverse media publicity impact on prescribing of paroxetine and the notification of suspected adverse drug reactions? Analysis of routine databases, 2001-2004. Br J Clin Pharmacol 2006 61(2):224-228.
21 Slovic P. The Perception of risk. 2011th ed. London: Earthscan; 2000.
22 Ruiter, R, Visser, L.V., Van Herk-Sukel, M.P., Geelhoed-Duijvestijn, P.H., De Bie, S., Straus, S.M. Prescribing of rosiglitazone and pioglitazone following safety signals: analysis of trends in dispensing patterns in the Netherlands from 1998 to 2008. Drug Saf 2012 35(6):471-80.
23 Cheung A, Sacks D, Dewa CS, Pong J, Levitt A. Pediatric prescribing practices and the FDA black-box warning on antidepressants. J Dev Behav Pediatr 2008 29(3):213-215.
24 Karpel JP, Peters JI, Szema AM, Smith B, Anderson PJ. Differences in physicians' self-reported knowledge of, attitudes toward, and responses to the black box warning on long-acting beta-agonists. Ann Allergy Asthma Immunol 2009 103(4):304-310.
25 Ko Y, Malone DC, Skrepnek GH, Armstrong EP, Murphy JE, Abarca J, et al. Prescribers' knowledge of and sources of information for potential drug-drug interactions: A postal survey of US prescribers. Drug Saf 2008 31(6):525-536.
26 Sino CG, Munnik A, Schuurmans MJ. Knowledge and perspectives of Dutch home healthcare nurses regarding medication frequently used by older people. International Journal of Older People Nursing 2012 Epub ahead of print July 16.
27 Crouch S, Robinson P, Pitts M. A comparison of general practitioner response rates to electronic and postal surveys in the setting of the National STI Prevention Program. Aust N Z J Public Health 2011 35(2):187-189.
28 Suttle CM, Jalbert I, Alnahedh T. Examining the evidence base used by optometrists in Australia and New Zealand. Clin Exp Optom 2012 95(1):28-36.
29 Johnson TP, Wislar JS. Response rates and nonresponse errors in surveys. J Am Med Assoc 2012 05;307(17):1805-1806.
30 Dutch Ministry of Health, Welfare and Sports. BIG register. Cijfers. (Only available in Dutch). 2011; Available at: http://www.bigregister.nl/overbigregister/cijfers/. Accessed 24 January, 2013.
31 Netherlands Institute for Health Services Research (NIVEL). Beroepen in de gezondheidszorg. Databank. 2011; Available at: http://www.nivel.nl/databank. Accessed 24 January, 2013.
32 Goossens L, Knoester P, Rutten-Van Molken M. Avastin (bevacizumab), Macugen (pegaptanib) and Lucentis (ranibizumab): Comparison of medication costs. Pharm Weekbl 2008 04;143(16):75-79.

33 Deschepper R, Grigoryan L, Lundborg CS, Hofstede G, Cohen J, Kelen GVD, et al. Are cultural dimensions relevant for explaining cross-national differences in antibiotic use in Europe? BMC Health Serv Res 2008 8.

34 Grigoryan L, Burgerhof JGM, Degener JE, Deschepper R, Lundborg CS, Monnet DL, et al. Attitudes, beliefs and knowledge concerning antibiotic use and self-medication: A comparative European study. Pharmacoepidemiol Drug Saf 2007 16(11):1234-1243.

35 Slovic P. Perceived risk, trust, and democracy. Risk Anal 1993 13(6):675-682.

36 European Medicines Agency. Benefit-risk methodology project. Work package 1 report: description of the current practice of benefit-risk assessment for centralised procedure products in the EU regulatory network. 2011; Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/07/WC500109478.pdf. Accessed 24 January 2013.

37 Walaski P. Risk and Crisis Communications : Methods and Messages. Hoboken, NJ, USA: John Wiley & Sons, Inc.; 2011.

38 McComas KA. Defining moments in risk communication research: 1996-2005. J Health Commun 2006 11(1):75-91.

39 Renn O. Three decades of risk research: accomplishments and new challenges. Journal of Risk Research 1998 1(1):49-71.

40 Bostrom A, Lofstedt RE. Communicating risk: Wireless and hardwired. Risk Anal 2003 23(2):241-248.

41 Fischhoff B, Brewer NT, Downs JS. Communicating risks and benefits. An evidence-based user's guide. 2011; Available at: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM268069.pdf. Accessed 16 February 2013.

42 Ubel PA, Angott AM, Zikmund-Fisher BJ. Physicians recommend different treatments for patients than they would choose for themselves. Arch Intern Med 2011 171(7):630-634.

43 A. H. Arnardottir. Regulatory benefit-risk assessment. Different perspectives. University Medical Center Groningen, University of Groningen. 2012.

44 Ropeik D, Slovic P. Risk communication: a neglected tool in protecting public health. Risk in Perspective 2003 11(2).

45 Slovic P. Perception of risk. Science 1987 236(4799):280-5.

46 Festinger L. A theory of cognitive dissonance. Stanford: Stanford University Press; 1957.

47 Lofstedt RE. The impact of the Cox-2 inhibitor issue on perceptions of the pharmaceutical industry: Content analysis and communication implications. J Health Commun 2007 12(5):471-491.

48 Piening S, Haaijer-Ruskamp FM, De Graeff PA, Straus SMJM, Mol PGM. Healthcare professionals self-reported experiences and preferences related to direct healthcare professional communications: A survey conducted in the Netherlands. Drug Saf 2012 35(11):1061-1072.

49 Kasperson RE, Renn O, Slovic P, Brown HS, Emel J, Goble R, et al. The social amplification of risk: A conceptual framework. Risk Anal 1988 8(2):177-187.

50 Mazor KM, Andrade SE, Auger J, Fish L, Gurwitz JH. Communicating safety information to physicians: An examination of dear doctor letters. Pharmacoepidemiol Drug Saf 2005 14(12):869-875.

51 Fischhoff B. Risk Perception and Communication Unplugged - 20 Years of Process. Risk Analysis 1995 15(2):137-145.

52 Fischhoff B. Why (cancer) risk communication can be hard. J Natl Cancer Inst Monographs 1999 (25):7-13.
53 Lundgren, R.E. & McMakin, A.H. Risk Communication. A handbook for communicating environmental, safety, and health risks. Third edition. ed. Columbus, Ohio, USA.: Battelle Press; 2004.
54 Morrato EH, Curbow B, Crum RM, Nowels C, Feinleib M. Communicating drug risk to physicians: Challenges and opportunities. Int J Risk Saf Med 2008 20(3):143-154.
55 Bahri P. Public pharmacovigilance communication: A process calling for evidence-based, objective-driven strategies. Drug Saf 2010 33(12):1065-1079.
56 Edwards B, Chakraborty S. Risk communication and the pharmaceutical industry: What is the reality? Drug Saf 2012 35(11):1027-1040.
57 Slovic P, Peters E, Grana J, Berger S, Dieck GS. Risk perception of prescription drugs: Results of a national survey. Drug Inf J 2007 41(1):81-100.
58 Campbell WH, Califf RM. Improving communication of drug risks to prevent patient injury: Proceedings of a workshop. Pharmacoepidemiol Drug Saf 2003 12(3):183-194.
59 Prieto L, Spooner A, Hidalgo-Simon A, Rubino A, Kurz X, Arlett P. Evaluation of the effectiveness of risk minimization measures. Pharmacoepidemiol Drug Saf 2012 21(8):896-899.
60 Wood AJJ. If you don't know where you are going, you can't tell if you have arrived: Defining goals for drug safety announcements. Clin Phar Ther 2013 93(4):302-303.
61 Fischhoff B, Lichtenstein S, Slovic P, Derby SL, Keeney RL. Acceptable Risk. Cambridge.: Cambridge University Press.; 1981.
62 Seligman PJ, Osborne SF. Perspectives on early communication of drug risks to the public. Clin Pharmacol Ther 2009 85(3):335-339.

Nederlandse samenvatting

Dit proefschrift richt zich op risicocommunicatie over veiligheidproblemen van geneesmiddelen. Gedurende de levenscyclus van een geneesmiddel dat op de markt is toegelaten kunnen zich ernstige veiligheidsproblemen voordoen.[1-3] Deze problemen kunnen leiden tot ziekenhuisopnamen, handicaps, of zelfs overlijden van patiënten.[4,5] Zorgverleners dienen van deze kwesties op de hoogte te worden gebracht. In Europa wordt dit voornamelijk gedaan door middel van papieren brieven; zogenaamde Direct Healthcare Professional Communications (DHPC's). Deze waarschuwingsbrieven worden verstuurd door het farmaceutische bedrijf op instigatie van de nationale autoriteiten en/of het Europees Geneesmiddelenbureau (EMA). De brieven zijn gericht op het waarborgen van veilig en doelmatig gebruik van geneesmiddelen.[6] DHPC's zijn echter niet altijd succesvol geweest in het effectief communiceren van veiligheidsinformatie aan zorgverleners.[7-9] De nieuwe farmacovigilantie wetgeving die van kracht werd in juli 2012, bepaalt dat het effect van risico beperkende maatregelen moet worden gemeten.[10,11] Een referentiekader met betrekking tot de effecten van DHPC's op de klinische praktijk is noodzakelijk. Dit referentiekader kan worden verkregen door het effect van voorgaande risico beperkende maatregelen te bepalen.[12] Een dergelijk overzicht ontbrak in het debat over de effectiviteit van DHPC's. Ook waren de ervaringen en voorkeuren van Nederlandse zorgverleners met betrekking tot de DHPC onbekend.

Daarom zijn de belangrijkste doelstellingen van het 'Communicating Risk Effectively' (CORE) project:

- Een overzicht bieden van de impact van DHPC's en exploreren welke determinanten bepalend zijn voor deze impact. (Deel 1, hoofdstukken 2, 3, 4)
- De ervaringen en voorkeuren verkennen van Nederlandse zorgverleners met betrekking tot de DHPC en de toegevoegde waarde bepalen van een nieuwe risico communicatiemethode, gebaseerd op deze voorkeuren. (Deel 2, hoofdstukken 5, 6)

In dit hoofdstuk bespreken we de belangrijkste bevindingen van het CORE project, de methodologische overwegingen, en de implicaties van het onderzoek voor de huidige praktijk en voor toekomstig onderzoek.

Belangrijkste bevindingen

Deel 1 - De impact van veiligheidswaarschuwingen

In **hoofdstuk 2** worden de resultaten gegeven van het systematische literatuuronderzoek dat is uitgevoerd met behulp van de online literatuurzoekmachines Medline en Embase.

We gaven een overzicht van studies die de impact van de DHPC, Black Box waarschuwingen en 'Public Health Advisories' hebben onderzocht. De zoekactie resulteerde in 52 relevante artikelen. De studies waren voornamelijk gebaseerd op twee geneesmiddelengroepen, namelijk de derde generatie orale anticonceptiva (verhoogd risico op trombose) en selectieve serotonine heropname remmers (risico op zelfmoord bij adolescenten en kinderen) en één geneesmiddel, namelijk cisapride (risico op ernstige hartritmestoornissen). De overige artikelen beschreven een breed scala aan geneesmiddelen en geneesmiddelgroepen. Van bijna de helft van de studies was de onderzoeksopzet inadequaat (voor/na studies) en heterogeniteit in de analyses belemmerde de rapportage van algehele effecten. In studies waarin gebruik werd gemaakt van tijdsreeksanalyses werd melding gemaakt van een meer gemengde impact van veiligheidswaarschuwingen dan in voor/na-studies. Ongewenste effecten werden onderzocht in studies betreffende selectieve serotonine heropname remmers (zelfmoord, afname in gebruik door volwassenen) en de derde generatie orale anticonceptiva (conceptie, abortus). Deze ongewenste effecten waren bijna altijd aanwezig, waarmee het belang van anticiperen op niet alleen de gewenste, maar ook de ongewenste effecten van veiligheidswaarschuwingen is aangetoond. We concludeerden dat veiligheidswaarschuwingen invloed op de klinische praktijk kunnen hebben. Harde conclusies zijn echter moeilijk te trekken. De resultaten toonden aan dat aanvullend onderzoek nodig is waarin gebruik gemaakt wordt van passende onderzoeksopzetten en statistische analyses om de impact van veiligheidswaarschuwingen volledig te begrijpen.

De impact van een grote groep Nederlandse DHPC's op geneesmiddelgebruik werd geëvalueerd in **hoofdstuk 3**. Landelijke gegevens van verstrekte geneesmiddelen werden beoordeeld voor de periode 2000-2008 voor nieuwe gebruikers van geneesmiddelen waarvoor één of meer DHPC's zijn verstuurd. Negenenvijftig DHPC's werden geïncludeerd, verstuurd voor 46 geneesmiddelen of geneesmiddelgroepen. Effecten op korte termijn gebruik werden geëvalueerd met regressiemodellen en de aanwezigheid van veranderingen in gebruik op lange termijn met tijdreeksanalyses waarin bestaande trends werden ingecalculeerd. Op de korte termijn (in het jaar na de DHPC werd verzonden) zagen we voor bijna de helft van de geneesmiddelen een daling van het gebruik vergeleken met het jaar ervoor. Langdurige veranderingen in gebruik werden geobserveerd voor een derde van de geneesmiddelen, wat resulteerde in een gemiddelde afname in gebruik van 27%, variërend van -10% tot -67%. Veranderingen in het gebruik waren niet duidelijk gerelateerd aan reeds bestaande trends.

Op basis van deze resultaten concludeerden we dat veiligheidswaarschuwingen een afname in gebruik veroorzaken in bijna de helft van de gevallen op de korte termijn en in

één derde van de gevallen op de lange termijn. Mogelijke factoren van invloed op de impact op het gebruik zouden kunnen zijn: het type en de ernst van de bijwerking, beschikbaarheid van alternatieve geneesmiddelen, het type voorschrijver en de medische noodzaak van het geneesmiddel.

Om de invloed van deze determinanten vast te stellen hebben we in **hoofdstuk 4** nader onderzocht welke kenmerken de invloed van de DHPC bepalen. We includeerden dezelfde 59 DHPC die voor 46 geneesmiddelen werden verzonden tussen 2001 en 2008. Met behulp van meervoudige lineaire regressie hebben we de impact onderzocht van de volgende determinanten op de relatieve verandering van geneesmiddelgebruik: de tijd tot de DHPC vanaf de datum van registratie van het geneesmiddel, de trend in het gebruik in de 12 maanden voorafgaand aan de DHPC, de mate van therapeutische innovatie van het geneesmiddel, of het geneesmiddel aanvankelijk werd voorgeschreven door een specialist of niet, of het een eerste of een herhaalde DHPC betrof, de beschikbaarheid van een standaard DHPC sjabloon op het moment dat de DHPC is afgegeven en het type bijwerking. We zagen dat DHPC's minder invloed hadden op het gebruik van specialistische geneesmiddelen dan op het gebruik van niet-specialistische geneesmiddelen. DHPC's die werden verstuurd nadat de standaard sjabloon was gepubliceerd waarin het veiligheidsprobleem werd benadrukt droegen bij aan een lager gebruik. DHPC's verstuurd in verband met onomkeerbare, potentieel fatale veiligheidsproblemen[13] (risico op overlijden en invaliditeit) waren geassocieerd met een lager gebruik. Een marginaal significant effect werd gevonden voor geneesmiddelen met een afnemende trend in gebruik voordat de DHPC werd verzonden. Er werd geen significant effect waargenomen voor de mate van de therapeutische innovatie, herhaalde DHPC's, en veiligheidsproblemen met een risico op ziekenhuisopname. Deze determinanten verklaren gezamenlijk 39% van de totale variantie in de verandering van geneesmiddelgebruik. De studie vormt een eerste verkenning van determinanten die de impact van DHPC's beïnvloeden.

We concludeerden dat risicocommunicatie over veiligheidsproblemen van geneesmiddelen effectief kan zijn, met name in het geval van goed gestructureerde informatie en zeer ernstige veiligheidsproblemen. De effectiviteit van DHPC's kan worden geoptimaliseerd door DHPC's hierop af te stemmen en door andere communicatiekanalen toe te voegen, bijvoorbeeld voor geneesmiddelen die vaker worden voorgeschreven nadat een DHPC is verzonden.

Deel 2 - Op weg naar optimalisatie van het effect van veiligheidswaarschuwingen; een focus op Direct Healthcare Professional Communications.

In **hoofdstuk 5** hebben we een vragenlijst ontwikkeld en getest om ervaringen met DHPC's en voorkeuren van Nederlandse zorgverleners te bepalen. De vragenlijst en twee herinneringen werden vervolgens verstuurd naar een aselecte steekproef van ongeveer 3.500 Nederlandse huisartsen, internisten, openbare- en ziekenhuisapothekers. Een derde van hen stuurde de vragenlijst ingevuld terug. Hoewel de meerderheid van de zorgverleners risico-informatie over geneesmiddelen als belangrijk beschouwde, was een substantiële groep niet bekend met de DHPC als methode van informatieverstrekking. Apothekers bleken meer bewust van veiligheidsproblemen en ondernamen meer actie dan artsen. De respondenten identificeerden voornamelijk andere kanalen dan de DHPC als bron voor hun kennis over een aantal recente veiligheidsproblemen. De studie toonde ook aan dat de zorgverleners meer vertrouwen hadden in veiligheidsinformatie afkomstig van het College ter Beoordeling van Geneesmiddelen (CBG) dan van de farmaceutische industrie. De respondenten waren van mening dat de veiligheidsinformatie bij voorkeur dient te worden verstrekt door een onafhankelijke bron, zoals het CBG, of de eigen beroepsvereniging. De verkozen alternatieve kanalen van veiligheidsinformatie waren e-mail, medische tijdschriften, en geautomatiseerde voorschrijfsystemen.

We concludeerden dat veiligheidsinformatie over geneesmiddelen de zorgverlener niet altijd bereikt via DHPC's en dat additionele inspanningen nodig zijn, voornamelijk om huisartsen te bereiken. Alternatieve en/of aanvullende risicocommunicatie methoden dienen op elektronische wijze of via medische tijdschriften plaats te vinden. Bovendien dient (additionele) risicocommunicatie door een onafhankelijke bron, zoals het CBG, te worden overwogen.

In **hoofdstuk 6** rapporteren we de resultaten van een pilotstudie die werd verricht om de additionele waarde te bepalen van een e-mail die door het CBG is verzonden voor het geneesmiddel pegaptanib. We voerden een gerandomiseerde gecontroleerde studie uit waarin de interventiegroep zowel de pegaptanib DHPC, als een e-mail gestuurd werd. De controlegroep kreeg enkel de traditionele papieren DHPC. Na twee weken ontvingen beide groepen een uitnodiging voor deelname aan een online vragenlijstonderzoek. Vragen werden gesteld over de kennis en de perceptie van de respondenten over de pegaptanib kwestie en actie die zij naar aanleiding daarvan hadden genomen. Extra vragen werden gesteld over hun tevredenheid met de DHPC en de e-mail. Veertig respondenten vulden de vragenlijst in. Respondenten die de extra e-mail ontvingen waren beter geïnformeerd over het pegaptanib veiligheidsprobleem en zij namen vaker maatregelen dan de respondenten die alleen de papieren DHPC ontvingen. De kwestie

werd door de meeste respondenten besproken met collega's. De meerderheid van de respondenten in zowel de interventiegroep als de controlegroep gaf aan dat ze in de toekomst graag een e-mail zouden ontvangen met veiligheidsinformatie over geneesmiddelen. De respondenten ontvangen zowel de DHPC als de e-mail bij voorkeur van het CBG. We concludeerden dat het versturen van een additionele e-mail effectiever is gebleken dan het versturen van enkel een papieren DHPC. Respondenten waren beter op de hoogte van het veiligheidsprobleem en ondernamen meer actie naar aanleiding van de kwestie.

Methodologische overwegingen

Nieuw geneesmiddelgebruik als uitkomstmaat om de impact van DHPC's te beoordelen
In **hoofdstuk 3** en **hoofdstuk 4** hebben we ons gericht op nieuw geneesmiddelgebruik als uitkomstmaat om de impact van DHPC's te beoordelen. Opgemerkt dient te worden dat een afname in gebruik niet altijd het beoogde effect van een DHPC behoeft te zijn.[14-16] Het effect van DHPC's dient tevens te worden geanalyseerd met behulp van uitkomstmaten die direct zijn gerelateerd aan het veiligheidsprobleem, zoals aangegeven in **hoofdstuk 1**. Dergelijke uitkomstmaten zijn bijvoorbeeld; gelijktijdig gebruik van gecontra-indiceerde geneesmiddelen[17] of hoe vaak zorgverleners laboratoriumtests aanvragen om vroegtijdig mogelijke toxiciteit van een geneesmiddel te identificeren.[18] De resultaten van dit onderzoek kunnen slechts worden gebruikt om te anticiperen op de impact van DHPC's op nieuwe geneesmiddelgebruik. Alle andere maatregelen die gebaseerd worden op deze resultaten moeten zorgvuldig worden overwogen. Desondanks zijn wij van mening dat nieuw geneesmiddelgebruik een geschikte uitkomstmaat is om de rol van determinanten van effecten van DHPC verkennen. Het is een uitkomstmaat die betrouwbaar kan worden beoordeeld voor een grote groep van geneesmiddelen. Nieuw geneesmiddelgebruik is tevens een meer gevoelige maat dan het totale gebruik, aangezien veranderingen in het voorschrijfgedrag sneller verwacht kunnen worden bij nieuwe gebruikers.[19] Classificatie van de gewenste en verwachte effecten had een analyse van de impact van DHPC's op meer specifieke uitkomstmaten kunnen faciliteren. Een dergelijke classificatie zou echter alleen mogelijk zijn geweest indien vastgesteld in een prospectieve setting, voorafgaand aan de verzending van de DHPC. De studies beschreven in **hoofdstuk 3 en 4** kunnen worden beschouwd als uitgangspunt voor toekomstige studies. Deze studies kunnen meer specifieke uitkomstmaten evalueren welke zijn afgestemd op de aanbevelingen omschreven in de DHPC.

Beperkt aantal determinanten

In **hoofdstuk 4** hebben we een reeks van zeven determinanten geïncludeerd om te beoordelen welke kenmerken de invloed van Nederlandse DHPC's bepalen. We hebben het aantal determinanten moeten beperken als gevolg van de steekproefgrootte. Ons volledige model verklaart 39% van de totale variantie in de verandering van geneesmiddelgebruik. Andere factoren die niet zijn opgenomen in ons model dragen hier wellicht ook aan bij, zoals bijvoorbeeld media-aandacht, de incidentie van de veiligheidsproblemen, veiligheidsproblemen gerelateerd aan off-label gebruik en de beschikbaarheid van alternatieve geneesmiddelen. Er is gesuggereerd dat media aandacht een belangrijke rol zou kunnen spelen bij de impact van de DHPC.[20-22] Eerder voerden wij een exploratieve zoekactie uit onder leken- en vakliteratuur voor een selectie van de DHPC's in ons onderzoek. Dit leverde te weinig informatie op om de aanwezigheid van media-aandacht te includeren in ons model. De incidentie van veiligheidsproblemen kon eveneens niet worden geïncludeerd, omdat het in de meerderheid van de DHPC's niet werd genoemd. DHPC's verzonden in verband met veiligheidsproblemen gerelateerd aan 'off-label' gebruik waren te gering in aantal, wat zorgde voor onvoldoende variatie binnen de variabele voor inclusie in ons model. Alternatieve geneesmiddelen waren beschikbaar voor bijna alle geneesmiddelen en dit aspect werd indirect geïncludeerd in de innovatie variabele. DHPC's verzonden voor meer innovatieve geneesmiddelen hadden geen grotere impact op het gebruik dan minder innovatieve geneesmiddelen. Daarom lijkt het onwaarschijnlijk dat de beschikbaarheid van een alternatieve behandeling een belangrijke determinant zou zijn. Het probleem van het beperkte aantal determinanten kan worden aangepakt door deze studie te herhalen op een moment dat er meer DHPC's zijn verzonden waardoor het mogelijk wordt meer determinanten in een vergelijkbaar model te includeren. Op dit moment kan onze studie worden beschouwd als een eerste verkenning van determinanten die de impact van DHPC beïnvloeden. Verdere bevestiging en uitbreiding van deze studies is gerechtvaardigd.

Generaliseerbaarheid

In de studies beschreven in **hoofdstuk 3** en **hoofdstuk 4** is een groot aantal DHPC opgenomen welke zijn verzonden gedurende een periode van acht jaar. De DHPC's besloegen een breed scala van veiligheidsproblemen en geneesmiddelen die alle grote therapeutische klassen vertegenwoordigden die worden voorgeschreven in de ambulante zorg. Uniformiteit van de methode om impact van DHPC beoordelen maakte de vergelijking van de effecten van de verschillende DHPC's mogelijk en verhoogde de generaliseerbaarheid van de resultaten.

De vrij lage respons van de studies beschreven in **hoofdstuk 5** en **hoofdstuk 6** beperkt de generaliseerbaarheid van de resultaten. Ondanks het verzenden van twee herinneringen in beide studies, reageerde slechts 34% en 19% (respectievelijk) van de zorgverleners. Lage respons bij enquêtes onder zorgverleners is niet ongewoon als gevolg van bijvoorbeeld toenemende werkdruk, 'vragenlijst vermoeidheid' en een lage prioriteit van het invullen van vragenlijsten, voornamelijk onder artsen.[23-29] Desondanks kan de lage respons onze resultaten hebben vertekend in de zin dat zorgverleners die zich niet bewust zijn van, of niet geïnteresseerd zijn in DHPC's, ondervertegenwoordigd zijn in onze steekproeven. Dit zou kunnen betekenen dat in de dagelijkse praktijk nog minder beroepsbeoefenaren in de gezondheidszorg zich bewust zijn van DHPC en specifieke veiligheidsproblemen dan waargenomen in onze studie, wat de noodzaak van verbeteringen in de huidige risicocommunicatie onderstreept. Johnson en Wislar verklaarden dat de respons wellicht niet zo sterk geassocieerd is met de kwaliteit en de representativiteit van een enquête en benadrukten het belang van het selecteren van een representatieve steekproef van de bevolking.[29] In **hoofdstuk 5** konden we geen kenmerken van non-respondenten analyseren wegens het anonieme karakter van de vragenlijst. We konden slechts melden dat onze steekproef representatief was voor de Nederlandse setting op het gebied van sekse,[30] en het percentage van de huisartsen die in deeltijd werken.[31] We vonden geen significante verschillen tussen vroege en late respondenten, op twee variabelen na. Het is mogelijk dat non-respondenten andere voorkeuren hebben dan respondenten betreffende de apothekers en de farmacotherapie vergaderingen als bron van veiligheidsinformatie. Buiten deze twee variabelen zijn de resultaten van deze studie naar alle waarschijnlijkheid niet beïnvloed door non-response bias. In **hoofdstuk 6** werden bij vergelijking van de respondenten met de non-respondenten met betrekking tot geslacht, beroep en type ziekenhuis geen significante verschillen waargenomen. De lage respons in deze studie kan worden toegeschreven aan het beperkte gebruik van pegaptanib in Nederland.[32] Elf zorgverleners reageerden op de uitnodiging voor deelname aan onze enquête door te stellen dat zij de vragenlijst niet zouden invullen, omdat ze pegaptanib niet toedienen of verstrekken. Vijfentwintig respondenten die de vragenlijst invulden gaven hetzelfde aan. Dit benadrukt het belang van een pilotstudie die als basis kan dienen voor gedegen steekproefgrootte berekeningen in het geval een vragenlijstonderzoek de voorkeur geniet om de impact van veiligheidswaarschuwingen te evalueren.

Het is niet duidelijk in welke mate de resultaten van onze studies gegeneraliseerd kunnen worden naar andere landen. We evalueerden de invloed van de Nederlandse DHPC en de ervaringen van Nederlandse zorgverleners. In de meeste gevallen is dezelfde DHPC, zij het vertaald, verzonden in heel Europa, in het bijzonder in het geval van

geneesmiddelen die zijn geregistreerd op Europees niveau. Echter, zorgverleners in de diverse Europese landen kunnen verschillend reageren op de DHPC. Risicoperceptie kan uiteenlopen en culturele verschillen met betrekking tot geneesmiddelgebruik kunnen bestaan.[33,34] Vertrouwen in instituties bijvoorbeeld, één van de factoren die bepalen hoe een risico wordt ervaren kan variëren van land tot land, zoals de interpretatie van voordelen en risico's van geneesmiddelen bleek te verschillen tussen diverse nationale geneesmiddelautoriteiten.[35,36] Een bericht wordt niet gehoord, geloofd en opgevolgd als het vertrouwen in en de geloofwaardigheid van de bron van de informatie ter discussie wordt gesteld.[37] Dit kan betekenen dat zorgverleners in bepaalde andere landen er de voorkeur aan geven om de veiligheidsinformatie over geneesmiddelen niet te ontvangen van de nationale geneesmiddelenautoriteit. Dit zou benadrukken dat elke situatie apart moet worden beoordeeld. Een EU-breed onderzoek zou een vergelijking van de (determinanten van) impact van DHPC's in verschillende landen mogelijk maken evenals een vergelijking van de ervaringen en voorkeuren van zorgverleners met betrekking tot de DHPC. Hiermee kan informatie verkregen worden over de noodzaak van specifieke nationale risicocommunicatie strategieën.

Toekomstig onderzoek

Beoordeling van de impact van veiligheidsmaatregelen

Uit de resultaten van onze systematische review blijkt een duidelijke behoefte aan nader onderzoek om de impact van veiligheidsmaatregelen volledig te kunnen begrijpen. De impact van DHPC's kan niet alleen worden bepaald door het geneesmiddelgebruik te analyseren. Uitkomstmaten die meer specifiek zijn afgestemd op de veiligheidskwestie moeten ook worden geanalyseerd. Clusters van DHPC's met dezelfde aanbeveling kunnen meer inzicht geven in de te verwachten gevolgen van DHPC's voor meer specifieke uitkomstmaten. Dergelijke analyses kunnen worden gefaciliteerd door de aanbevelingen die in de DHPC worden gegeven prospectief te classificeren.

Verschillende andere factoren die ook van invloed zouden kunnen zijn op de impact van de DHPC werden niet geïncludeerd in het model dat werd beschreven in **hoofdstuk 4**. Over een aantal jaar, wanneer er meer DHPC zijn verzonden, en de inhoud van de DHPC zo mogelijk nog verder is geoptimaliseerd, kan dit onderzoek worden herhaald. Andere factoren kunnen dan ook worden opgenomen in een model en het probleem van de beperkte steekproefomvang kan hiermee worden opgelost.

Zowel de gewenste als de verwachte ongewenste effecten van veiligheidswaarschuwingen moeten worden beoordeeld. Tijdreeksanalyse is hiervoor het meest geschikt, omdat het zorgt voor een grotere betrouwbaarheid bij de beoordeling van

de impact van veiligheidswaarschuwingen in vergelijking met een voor/na onderzoeksopzet. Tevens dienen alle waarschuwingen die worden afgegeven voor een geneesmiddel individueel beoordeeld te worden in plaats van slechts een selectie van waarschuwingen en rapportage van een algeheel effect. Op deze wijze wordt het mogelijk om kennis te vergaren over het type waarschuwing dat de gewenste gedragsverandering van zorgverleners het meest effectief kan faciliteren.

Optimalisatie van de impact van veiligheidswaarschuwingen

Voornamelijk naar communicatie over milieu gerelateerde risico's is reeds veel onderzoek uitgevoerd, waarvan de resultaten kunnen worden gebruikt bij het verbeteren van de communicatie over veiligheidsproblemen van geneesmiddelen.[38-40] Onze studies waren gericht op het verkrijgen van empirisch bewijs voor een aantal belangrijke aspecten van het risico communicatie. Deze bevindingen dragen bij aan de praktische benadering die staat beschreven in een praktische handleiding over de wijze waarop gezondheidscommunicatieprogramma's gepland, geïmplementeerd en geëvalueerd dienen te worden.[41] Met betrekking tot enquêtes, dient een lage respons te worden verwacht; vooral in geval van online enquêtes. Pilotonderzoeken moeten worden uitgevoerd om een basis te bieden voor grondige berekeningen van de steekproefgrootte.

De respondenten van de studie beschreven in hoofdstuk 5 gaven aan dat ze graag informatie over veiligheidsproblemen van geneesmiddelen ontvangen via e-mail en van het CBG. Deze voorkeur hebben we op de proef gesteld in een gerandomiseerde klinische studie in **hoofdstuk 6**. Vergelijkbare gerandomiseerde klinische studies kunnen worden opgezet om de impact van een veiligheidswaarschuwing te beoordelen die wordt gecommuniceerd via andere zeer gewaardeerde communicatiebronnen of -kanalen. Deze methoden moeten worden gekozen op basis van het doel van risicocommunicatie, dat wil zeggen nieuwe informatie delen, opvattingen over voordelen en risico's van geneesmiddelen veranderend, of gedrag van zorgverleners veranderen. Vooral in het laatste geval zijn wellicht meer interventies nodig om op lange termijn veranderingen in het gedrag te bereiken.

Van de in **hoofdstuk 4**, **hoofdstuk 5** en **hoofdstuk 6** beschreven studies, weten we dat context er toe doet. Diverse risicoperceptie factoren (onomkeerbaarheid, hoog fataal risico en vertrouwen in instituties) spelen een rol in de manier waarop veiligheid van geneesmiddelen en de bijbehorende risico communicatie worden gepercipieerd door zorgverleners. Aangezien niet alle risicoperceptie factoren werden opgenomen in deze studies, is de invloed van andere factoren, zoals onzekerheid, begrip, en de ethische/morele aard niet bekend. Helaas is de meerderheid van het huidige onderzoek naar risicoperceptie uitgevoerd onder leken, en niet gerelateerd aan ernstige

veiligheidsproblemen van geneesmiddelen. Toekomstig onderzoek kan meer inzicht bieden, bijvoorbeeld door te bestuderen hoe artsen de voordelen en risico's afwegen bij het voorschrijven van geneesmiddelen waarvoor een DHPC is afgegeven. Leken beoordelen voordelen en risico's van diverse geneesmiddelen verschillend.[21] Hetzelfde valt te verwachten voor artsen. In het algemeen zijn mensen bereid om hogere risico's te nemen wanneer de voordelen groter zijn.[21] Met het feit dat artsen risico gerelateerde beslissingen maken voor hun patiënten, in plaats van voor zichzelf moet ook rekening worden gehouden. Het is aangetoond dat artsen risicovollere behandelingsopties voor zichzelf zouden kiezen dan voor hun patiënten.[42] Een andere studie suggereert dat toezichthouders, artsen en patiënten nieuwe ernstige risico's van een geneesmiddel op vergelijkbare wijze kunnen afwegen, wanneer deze worden gepresenteerd in de context van andere voordelen en risico's van een oraal anti-diabetes geneesmiddel. Een verhoogd, maar in absolute termen klein risico op blaaskanker van een hypothetisch oraal anti-diabetes medicijn had geen invloed op de keuze voor een geneesmiddel door alle drie de groepen.[43] Inzet van risicocommunicatie middelen als 'keuzehulpen' die gedeelde besluitvorming kunnen vergemakkelijken kan worden onderzocht wanneer verschillen in percepties over voordelen en risico's kunnen worden verwacht.

Beter begrip van de rol die risicoperceptie factoren spelen kan een leidraad vormen voor de optimalisering van het effect van toekomstige DHPC's.[44] Dit zal het beleid om risico communicatiemethoden te verbeteren, anticipatie op ongewenste effecten en ontwikkeling van nieuwe strategieën voor risicomanagement ondersteunen.[45] De impact van DHPC's die zijn verstuurd wegens andere dan administratieve kwesties en voor geneesmiddelen die op grotere schaal worden gebruikt, moeten ook worden beoordeeld. Specifieke aandacht moet worden besteed aan DHPC's waarmee nieuw geïdentificeerde veiligheidsproblemen worden gecommuniceerd, omdat deze nieuwe informatie zou kunnen botsen met de opvattingen die zorgverleners hebben over deze geneesmiddelen. Volgens de theorie van cognitieve dissonantie, kan dit ervoor zorgen dat zorgverleners deze nieuwe informatie buiten beschouwing laten.[45,46]

Implicaties voor regelgeving en praktijk

Risicocommunicatie krijgt meer en meer aandacht binnen het gebied van de geneesmiddelenbewaking, mede als gevolg van verhoogde aandacht voor transparantie. In 2007 kwam er een DHPC sjabloon beschikbaar en in 2012 werd de nieuwe farmacovigilantie wetgeving van kracht, waarin communicatie over risico's een belangrijke rol speelt.[6,10,11] Ondanks deze verbeteringen, kan er nog veel worden geleerd en geoptimaliseerd. Op basis van dit proefschrift, kunnen de volgende aanbevelingen worden

Tabel 1. Belangrijkste aanbevelingen

1.	**Verbeter communicatie methoden**
	Communiceer veiligheidsproblemen via een onafhankelijke, betrouwbare bron.
	Gebruik nieuwe communicatiekanalen, bijvoorbeeld e-mail om veiligheidsproblemen te communiceren.
	Zorg dat de DHPC opvalt voor zorgverleners, bijvoorbeeld door middel van een afbeelding van een gele hand op de envelop.
2.	**Vergroot betrokkenheid van zorgverleners**
	Betrek zorgverleners bij het opstellen van de DHPC's.
	Vergroot het bewustzijn onder zorgverleners over geneesmiddelautoriteiten.
	Licht zorgverleners voor over risicocommunicatie over veiligheidsproblemen.
3.	**Verbeter evaluatie van impact**
	Definieer en classificeer de beoogde effecten van DHPC's prospectief.
	Stel passende uitkomstmaten vast om de impact van DHPC's te beoordelen.
	Stel vast wanneer DHPC's als doeltreffend beschouwd kunnen worden.
	Anticipeer op ongewenste effecten van DHPC's.

gegeven (**Tabel 1**). Risicocommunicatie over veiligheidsproblemen van geneesmiddelen moet worden verbeterd door meerdere factoren aan te pakken.

1. Verbeter communicatie methoden

Vertrouwen speelt een belangrijke rol in het risicocommunicatieproces en farmaceutische bedrijven worden vaak gewantrouwd.[47,48] Een complex geheel van factoren speelt een rol in de opbouw en afbraak van vertrouwen en helaas is het makkelijker om vertrouwen te verliezen dan het te genereren of opnieuw op te bouwen zoals geschetst door het zogenaamde 'asymmetrie principe'.[35] Daarom raden wij aan veiligheidsproblemen van geneesmiddelen te communiceren via een betrouwbare bron, zoals het CBG.[49,50]
Nieuwe kanalen zoals e-mail kunnen worden gebruikt om veiligheid van geneesmiddelen te communiceren. Zorgverleners moeten kunnen aangeven of ze een dergelijke e-mail willen ontvangen voor alle geneesmiddelen of een selectie geneesmiddelen. Hiermee wordt het optreden van een zogenaamde 'waarschuwingsmoeheid' als gevolg van een overvloed aan informatie voorkomen.

In dit proefschrift hebben we niet bestudeerd of, en op welke wijze de inhoud van de DHPC kan worden verbeterd. Hoewel het effect van de DHPC over geneesmiddelgebruik al werd verhoogd na de beschikbaarheid van de standaard DHPC sjabloon, blijft verdere optimalisatie van de vorm en inhoud van de DHPC mogelijk. Het gebruik van symbolen is van essentieel belang om te

zorgen dat de DHPC opvalt bij zorgverleners.[49,50] Het is aanbevelenswaardig de brief te versturen met een extra symbool, zoals een foto van een oranje hand afgedrukt op de envelop. Dit gebeurt momenteel in Nederland in gevallen die onmiddellijk optreden van de zorgverlener vergen. Een andere kleur, bijvoorbeeld geel, kan worden gebruikt om de 'standaard DHPC' te onderscheiden van oranje hand gevallen waarin onmiddellijke actie door zorgverleners is vereist. Op de envelop van de DHPC en in de header van een eventuele e-mail dient het geneesmiddel en het veiligheidsprobleem in kwestie duidelijk te worden vermeld.

De belangrijkste informatie is niet altijd adequaat gepresenteerd in de DHPC en de leesbaarheid en duidelijkheid kunnen onvoldoende zijn.[50] De manier waarop aantallen worden gepresenteerd en risico's worden weergegeven heeft een grote invloed, zoals bijvoorbeeld de 'pil scare' heeft laten zien.[21,41,51,52] Dit zogenaamde 'framen' van risico's (bijvoorbeeld aangeven hoeveel patiënten zijn overleden versus hoeveel patiënten de bijwerkingen van het geneesmiddel hebben overleefd) lijkt leken en zorgverleners op vergelijkbare wijze te beïnvloeden.[21] Om de optimale weergave van risico's in DHPC te bereiken kan bestaand onderzoek onder leken worden bestudeerd. Zorgverleners hebben echter niet altijd dezelfde behoeften inzake risico-informatie als leken.[41] Bij het informeren van zorgverleners kan meer geavanceerde taal worden gebruikt, en referenties kunnen worden gegeven naar wetenschappelijke achtergrondinformatie.[53] Niettemin moet een zogenaamde polysemische boodschap (een boodschap die kan worden geïnterpreteerd op verschillende manieren) worden vermeden omdat het verwarring bij de doelgroep zou kunnen veroorzaken. De inhoud van de DHPC, met name de aanbevelingen, moet zo eenduidig mogelijk worden geformuleerd.[51,54,55] De belangrijkste aspecten van het veiligheidsprobleem, met inbegrip van de aanbevelingen, moeten eerst worden vermeld.[53] Om ongewenste effecten te voorkomen die kunnen worden veroorzaakt door een polysemisch bericht moet de inhoud van de DHPC vooraf getest worden door de doelgroep.[53]

2. Vergroot betrokkenheid van zorgverleners

Succesvolle risicocommunicatie is niet alleen afhankelijk van optimale communicatie methoden, maar ook van de betrokkenheid van de ontvanger. Idealiter vormt risicocommunicatie een tweerichtingsproces wat de noodzaak benadrukt van een nauwe betrokkenheid bij het opstellen van de DHPC van

zorgverleners die in de dagelijkse praktijk werken met het geneesmiddel in kwestie.[38,39,45,52,56,57] Ook beroepsverenigingen kunnen betrokken worden bij het opstellen van DHPC's en het informeren van hun leden, omdat ze hoog in het vaandel staan bij zorgverleners en worden beschouwd als geloofwaardige informatiebronnen.[52,54] Het is bekend hoe moeilijk het is om te voorspellen welke risico's voor andere personen relevant zijn.[41] Mits de juiste specifieke zorgverlener is betrokken men mag aannemen dat deze uit ervaring weet wat er al bekend is over het geneesmiddel en het veiligheidsprobleem en wat niet. Zij zijn zich bewust van de zorgen en behoeften en welke aspecten in de DHPC benadrukt dienen te worden.[41,52] Deze benadering kan mogelijk ongewenste effecten die optraden in het geval van de SSRI's voorkomen en situaties zoals de 'pill scare' zouden kunnen worden ingedamd.[51]

Een mogelijke aanpak is de 'Mental Models' methode.[52] Door zorgverleners en toezichthouders te interviewen kunnen hun meningen worden geïnventariseerd en eventuele verschillen kunnen gericht worden aangepakt. Deze aanpak is echter nogal tijdrovend, en wellicht meer bruikbaar als voorbereiding op de vorm en inhoud van DHPC's in het algemeen.[53] De methode is minder geschikt tijdens een crisissituatie waarin kostbare tijd verloren zou gaan. Verder zijn er diverse gevalideerde tests beschikbaar welke gebruikt kunnen worden om de leesbaarheid van DHPC testen op het gebied van zinsbouw, lengte van en het type gebruikte woorden.[41]

Zorgverleners zien een duidelijke rol voor toezichthoudende instanties in de communicatie van veiligheidsproblemen en de herkenbaarheid van deze instanties dient te worden verbeterd onder zorgverleners. Om zorgverleners te assisteren bij hun verantwoordelijkheid om op de hoogte te blijven van nieuwe geïdentificeerde veiligheidsproblemen van geneesmiddelen, moeten ze worden geïnformeerd over risicocommunicatie die zij gedurende hun carrière zullen ontvangen. Dit kan bijvoorbeeld tijdens de opleiding plaatsvinden, geïntegreerd met het onderwijs over de wijze waarop de veiligheidsproblemen gerapporteerd dienen te worden.

3. Verbeter evaluatie van impact

Risicocommunicatie kan op verschillende manieren worden geëvalueerd. Met behulp van zogenaamde formatieve evaluatie kan de inhoud van een bericht worden beoordeeld, procesevaluatie kan bijvoorbeeld worden gebruikt om te bepalen of het publiek een bericht heeft ontvangen en met uitkomst evaluatie kan worden bepaald of het beoogde effect van een bericht werd bereikt.[41]

De beoogde effecten van DHPC's moeten worden gedefinieerd en prospectief wordem geclassificeerd om na te kunnen gaan wat de meest geschikte uitkomstmaat is om de effectiviteit van de DHPC's te kunnen evalueren. Deze uitkomstmaten moeten bij voorkeur worden afgestemd op het veiligheidsprobleem, bijvoorbeeld gelijktijdig gebruik van gecontra-indiceerde geneesmiddelen,[17] of hoe vaak zorgverleners laboratoriumtests hebben aangevraagd om mogelijke toxiciteit van geneesmiddelen te identificeren.[18] Vervolgens is het belangrijk om te bepalen op welk punt een DHPC voldoende effectief kan worden beschouwd. Aangeven dat de invloed van risico beperkende maatregelen moeten worden geëvalueerd is alleen dan nuttig wanneer drempels worden gesteld en aanvullende maatregelen wordt gevraagd wanneer een dergelijke drempel niet is bereikt.[58-60] Dit zal niet gemakkelijk zijn, gezien het huidige gebrek aan informatie over de effectiviteit van deze maatregelen. Zo is het niet bekend of er een 'plafond effect' zou kunnen ontstaan wat een DHPC en alle additionele risicocommunicatie methoden zal belemmeren om nog meer impact te sorteren. Bovendien zijn er geen 'algemeen aanvaardbare risico's' vast te stellen, omdat het afhankelijk is van de context of het bereikte risicoreductie voldoende is.[61] Bij de DHPC betekent dit dat niet alle bijwerkingen voorkomen kunnen worden ondanks inachtneming van alle voorzorgsmaatregelen.[62] Het gemak waarmee drempelwaarden kunnen worden ingesteld is ook afhankelijk van het type uitkomstmaat. Deze kunnen vrij gemakkelijk worden bepaald voor het aantal geneesmiddelvoorschriften, of laboratoriumtesten. Maar het aantal bijwerkingen dat kan worden aanvaard, zou moeilijker zijn, rekening houdend met onderrapportage en mogelijke gelijkenis met symptomen van de ziekte in kwestie. De uitdaging in de nabije toekomst zal zijn om bewijzen te genereren die kunnen worden gebruikt om vast te stellen wat haalbaar is en wat niet. Voor elke DHPC moeten de mogelijke ongewenste effecten worden geverifieerd en gemonitord. Door te anticiperen op de ongewenste effecten, bijvoorbeeld door het geven van aanvullende informatie, kunnen problemen die zich hebben voorgedaan met selectieve serotonine heropname remmers (verminderd gebruik door volwassenen) en de derde generatie anticonceptiva (verhoogd aantal abortussen) wellicht worden vermeden in de toekomst.

Eindconclusie

Dit proefschrift geeft een overzicht van de impact van DHPC's en haar determinanten. Hoewel het lange termijn geneesmiddelgebruik daalde als gevolg van slechts een derde

van de DHPC's was deze daling aanzienlijk. De DHPC's bleken voornamelijk effectief in geval van goed gestructureerde informatie en zeer ernstige veiligheidsproblemen. Nederlandse zorgverleners gaven er de voorkeur aan om informatie over veiligheidsproblemen te ontvangen via elektronische kanalen en van een onafhankelijke bron. Een extra e-mail die werd verzonden door het College ter Beoordeling van Geneesmiddelen versterkte het effect van een schriftelijke DHPC door zorgverleners meer bewust te maken van het veiligheidsprobleem en meer actie te laten ondernemen naar aanleiding van de kwestie. Momenteel heeft de DHPC een duidelijke toegevoegde waarde. Eventuele toekomstige ontwikkelingen zullen moeten worden gemonitord. Vanuit een onbelemmerd onderzoeks-oogpunt, zijn aanbevelingen gedaan die kunnen worden gebruikt om de huidige communicatie over veiligheidsrisico's van geneesmiddelen te verbeteren. Beslissingen van toezichthouders worden beïnvloed door het bestuur van de gehele gezondheidszorgsector, wat de uitvoering van deze aanbevelingen kan bemoeilijken. Een flexibele houding van alle betrokkenen is vereist om veilig gebruik van geneesmiddelen te verbeteren die de volksgezondheid en uiteindelijk de patiënt ten goede zal komen.

Referenties

1 Mol PGM, Straus SMJM, Piening S, De Vries JTN, De Graeff PA, Haaijer-Ruskamp FM. A decade of safety-related regulatory action in the Netherlands: A retrospective analysis of direct healthcare professional communications from 1999 to 2009. Drug Saf 2010 33(6):463-474.

2 Giezen TJ, Mantel-Teeuwisse AK, Straus SMJM, Schellekens H, Leufkens HGM, Egberts ACG. Safety-related regulatory actions for biologicals approved in the United States and the European Union. J Am Med Assoc 2008 10;300(16):1887-1896.

3 Lasser KE, Allen PD, Woolhandler SJ, Himmelstein DU, Wolfe SM, Bor DH. Timing of new black box warnings and withdrawals for prescription medications. J Am Med Assoc 2002 05;287(17):2215-2220.

4 Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: Prospective analysis of 18 820 patients. Br Med J 2004 07;329(7456):15-19.

5 Sari AB-, Sheldon TA, Cracknell A, Turnbull A, Dobson Y, Grant C, et al. Extent, nature and consequences of adverse events: Results of a retrospective casenote review in a large NHS hospital. Qual Saf Health Care 2007 16(6):434-439.

6 European Commission. Volume 9A of the rules governing medicinal products in the European Union. Guidelines on Pharmacovigilance for medicinal products for human use. 2008; Available at: http://ec.europa.eu/health/files/eudralex/vol-9/pdf/vol9a_09-2008_en.pdf. Accessed 24 January, 2013.

7 Goldman SA. Communication of medical product risk: How effective is effective enough? Drug Saf 2004 27(8):519-534.

8 Woosley RL. Drug labeling revisions - Guaranteed to fail? J Am Med Assoc 2000 12;284(23):3047-3049.

9 Dusetzina SB, Higashi AS, Dorsey ER, Conti R, Huskamp HA, Zhu S, et al. Impact of FDA drug risk communications on health care utilization and health behaviors: A systematic review. Med Care 2012 50(6):466-478.

10 The European Parliament and The European Council. DIRECTIVE 2010/84/EU. 2010; Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0074:0099:EN:PDF. Accessed 24 January, 2013.

11 The European Parliament and The European Council. REGULATION (EU) No 1235/2010. 2010; Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0001:0016:EN:PDF. Accessed 24 January, 2013.

12 European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Module XV - Safety communication. 2012; Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500130396.pdf. Accessed 24 January, 2013.

13 Covello VT, Peters RG, Wojtecki JG, Hyde RC. Risk communication, the West Nile virus epidemic, and bioterrorism: Responding to the communication challenges posed by the intentional or unintentional release of a pathogen in an urban setting. Urban Health 2001 78(2):382-391.

14 Olfson M, Marcus SC, Druss BG. Effects of food and drug administration warnings on antidepressant use in a national sample. Arch Gen Psychiatry 2008 65(1):94-101.

15 Valuck RJ, Libby AM, Orton HD, Morrato EH, Allen R, Baldessarini RJ. Spillover effects on treatment of adult depression in primary care after FDA advisory on risk of pediatric suicidally with SSRIs. Am J Psychiatry 2007 164(8):1198-1205.
16 Williams D, Kelly A, Carvalho M, Feely J. Effect of the British warning on contraceptive use in the General Medical Service in Ireland. Ir Med J 1998 91(6):202-203.
17 Starner CI, Schafer JA, Heaton AH, Gleason PP. Rosiglitazone and pioglitazone utilization from January 2007 through May 2008 associated with five risk-warning events. J Managed Care Pharm 2008 14(6):523-531.
18 Willy ME, Manda B, Shatin D, Drinkard CR, Graham DJ. A Study of Compliance with FDA Recommendations for Pemoline (Cylert(registered trademark)). J Am Acad Child Adolesc Psychiatry 2002 41(7):785-790.
19 Wilkinson JJ, Force RW, Cady PS. Impact of safety warnings on drug utilization: Marketplace life span of cisapride and troglitazone. Pharmacotherapy 2004 24(8):978-986.
20 Martin RM, May M, Gunnell D. Did intense adverse media publicity impact on prescribing of paroxetine and the notification of suspected adverse drug reactions? Analysis of routine databases, 2001-2004. Br J Clin Pharmacol 2006 61(2):224-228.
21 Slovic P. The Perception of risk. 2011th ed. London: Earthscan; 2000.
22 Ruiter, R, Visser, L.V., Van Herk-Sukel, M.P., Geelhoed-Duijvestijn, P.H., De Bie, S., Straus, S.M. Prescribing of rosiglitazone and pioglitazone following safety signals: analysis of trends in dispensing patterns in the Netherlands from 1998 to 2008. Drug Saf 2012 35(6):471-80.
23 Cheung A, Sacks D, Dewa CS, Pong J, Levitt A. Pediatric prescribing practices and the FDA black-box warning on antidepressants. J Dev Behav Pediatr 2008 29(3):213-215.
24 Karpel JP, Peters JI, Szema AM, Smith B, Anderson PJ. Differences in physicians' self-reported knowledge of, attitudes toward, and responses to the black box warning on long-acting beta-agonists. Ann Allergy Asthma Immunol 2009 103(4):304-310.
25 Ko Y, Malone DC, Skrepnek GH, Armstrong EP, Murphy JE, Abarca J, et al. Prescribers' knowledge of and sources of information for potential drug-drug interactions: A postal survey of US prescribers. Drug Saf 2008 31(6):525-536.
26 Sino CG, Munnik A, Schuurmans MJ. Knowledge and perspectives of Dutch home healthcare nurses regarding medication frequently used by older people. International Journal of Older People Nursing 2012 Epub ahead of print July 16.
27 Crouch S, Robinson P, Pitts M. A comparison of general practitioner response rates to electronic and postal surveys in the setting of the National STI Prevention Program. Aust N Z J Public Health 2011 35(2):187-189.
28 Suttle CM, Jalbert I, Alnahedh T. Examining the evidence base used by optometrists in Australia and New Zealand. Clin Exp Optom 2012 95(1):28-36.
29 Johnson TP, Wislar JS. Response rates and nonresponse errors in surveys. J Am Med Assoc 2012 05;307(17):1805-1806.
30 Dutch Ministry of Health, Welfare and Sports. BIG register. Cijfers. (Only available in Dutch). 2011; Available at: http://www.bigregister.nl/overbigregister/cijfers/. Accessed 24 January, 2013.
31 Netherlands Institute for Health Services Research (NIVEL). Beroepen in de gezondheidszorg. Databank. 2011; Available at: http://www.nivel.nl/databank. Accessed 24 January, 2013.
32 Goossens L, Knoester P, Rutten-Van Molken M. Avastin (bevacizumab), Macugen (pegaptanib) and Lucentis (ranibizumab): Comparison of medication costs. Pharm Weekbl 2008 04;143(16):75-79.

33 Deschepper R, Grigoryan L, Lundborg CS, Hofstede G, Cohen J, Kelen GVD, et al. Are cultural dimensions relevant for explaining cross-national differences in antibiotic use in Europe? BMC Health Serv Res 2008 8.

34 Grigoryan L, Burgerhof JGM, Degener JE, Deschepper R, Lundborg CS, Monnet DL, et al. Attitudes, beliefs and knowledge concerning antibiotic use and self-medication: A comparative European study. Pharmacoepidemiol Drug Saf 2007 16(11):1234-1243.

35 Slovic P. Perceived risk, trust, and democracy. Risk Anal 1993 13(6):675-682.

36 European Medicines Agency. Benefit-risk methodology project. Work package 1 report: description of the current practice of benefit-risk assessment for centralised procedure products in the EU regulatory network. 2011; Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/07/WC500109478.pdf. Accessed 24 January 2013.

37 Walaski P. Risk and Crisis Communications : Methods and Messages. Hoboken, NJ, USA: John Wiley & Sons, Inc.; 2011.

38 McComas KA. Defining moments in risk communication research: 1996-2005. J Health Commun 2006 11(1):75-91.

39 Renn O. Three decades of risk research: accomplishments and new challenges. Journal of Risk Research 1998 1(1):49-71.

40 Bostrom A, Lofstedt RE. Communicating risk: Wireless and hardwired. Risk Anal 2003 23(2):241-248.

41 Fischhoff B, Brewer NT, Downs JS. Communicating risks and benefits. An evidence-based user's guide. 2011; Available at: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM268069.pdf. Accessed 16 February 2013.

42 Ubel PA, Angott AM, Zikmund-Fisher BJ. Physicians recommend different treatments for patients than they would choose for themselves. Arch Intern Med 2011 171(7):630-634.

43 A. H. Arnardottir. Regulatory benefit-risk assessment. Different perspectives. University Medical Center Groningen, University of Groningen. 2012.

44 Ropeik D, Slovic P. Risk communication: a neglected tool in protecting public health. Risk in Perspective 2003 11(2).

45 Slovic P. Perception of risk. Science 1987 236(4799):280-5.

46 Festinger L. A theory of cognitive dissonance. Stanford: Stanford University Press; 1957.

47 Lofstedt RE. The impact of the Cox-2 inhibitor issue on perceptions of the pharmaceutical industry: Content analysis and communication implications. J Health Commun 2007 12(5):471-491.

48 Piening S, Haaijer-Ruskamp FM, De Graeff PA, Straus SMJM, Mol PGM. Healthcare professionals self-reported experiences and preferences related to direct healthcare professional communications: A survey conducted in the Netherlands. Drug Saf 2012 35(11):1061-1072.

49 Kasperson RE, Renn O, Slovic P, Brown HS, Emel J, Goble R, et al. The social amplification of risk: A conceptual framework. Risk Anal 1988 8(2):177-187.

50 Mazor KM, Andrade SE, Auger J, Fish L, Gurwitz JH. Communicating safety information to physicians: An examination of dear doctor letters. Pharmacoepidemiol Drug Saf 2005 14(12):869-875.

51 Fischhoff B. Risk Perception and Communication Unplugged - 20 Years of Process. Risk Analysis 1995 15(2):137-145.

52 Fischhoff B. Why (cancer) risk communication can be hard. J Natl Cancer Inst Monographs 1999 (25):7-13.
53 Lundgren, R.E. & McMakin, A.H. Risk Communication. A handbook for communicating environmental, safety, and health risks. Third edition. ed. Columbus, Ohio, USA.: Battelle Press; 2004.
54 Morrato EH, Curbow B, Crum RM, Nowels C, Feinleib M. Communicating drug risk to physicians: Challenges and opportunities. Int J Risk Saf Med 2008 20(3):143-154.
55 Bahri P. Public pharmacovigilance communication: A process calling for evidence-based, objective-driven strategies. Drug Saf 2010 33(12):1065-1079.
56 Edwards B, Chakraborty S. Risk communication and the pharmaceutical industry: What is the reality? Drug Saf 2012 35(11):1027-1040.
57 Slovic P, Peters E, Grana J, Berger S, Dieck GS. Risk perception of prescription drugs: Results of a national survey. Drug Inf J 2007 41(1):81-100.
58 Campbell WH, Califf RM. Improving communication of drug risks to prevent patient injury: Proceedings of a workshop. Pharmacoepidemiol Drug Saf 2003 12(3):183-194.
59 Prieto L, Spooner A, Hidalgo-Simon A, Rubino A, Kurz X, Arlett P. Evaluation of the effectiveness of risk minimization measures. Pharmacoepidemiol Drug Saf 2012 21(8):896-899.
60 Wood AJJ. If you don't know where you are going, you can't tell if you have arrived: Defining goals for drug safety announcements. Clin Phar Ther 2013 93(4):302-303.
61 Fischhoff B, Lichtenstein S, Slovic P, Derby SL, Keeney RL. Acceptable Risk. Cambridge.: Cambridge University Press.; 1981.
62 Seligman PJ, Osborne SF. Perspectives on early communication of drug risks to the public. Clin Pharmacol Ther 2009 85(3):335-339.

Dankwoord

Iedereen die heeft bijgedragen aan de totstandkoming van dit proefschrift wil ik heel hartelijk danken.

Mijn promotie team bedank ik voor de grote betrokkenheid bij het CORE project, alle bijdragen aan het onderzoek en de snelle reacties op mijn vele verzoeken. Ondanks de verschillende achtergronden en visies denk ik dat dit samenwerkingsverband een gouden combinatie is gebleken. Ik heb erg veel van jullie geleerd.
Prof. Dr. Haaijer-Ruskamp, beste Floor, toen ik na je gastcollege bij de bachelorcursus Medische Sociologie met je in gesprek raakte had ik nooit verwacht dat ik nu onder jouw begeleiding mijn proefschrift zou afronden. Bedankt voor deze mogelijkheid en dat je me altijd weer bij de les wist te houden.
Prof. Dr. De Graeff, beste Pieter, ik ben je onder andere erg dankbaar dat je aandrong op het uitvoeren van de interventie studie. Ondanks de teleurstellende respons geeft de studie een belangrijk signaal en maakt het deze thesis tot een mooi afgerond geheel.
Dr. Straus, beste Sabine, je hebt geen idee wat je enthousiasme, waardering en motiverende woorden voor me hebben betekend de afgelopen jaren. Na elke bespreking in Den Haag of Utrecht kon ik er weer weken tegenaan. Mijn dank is groot.
Dr. Mol, beste Peter, hoewel ik me regelmatig heb gevoeld als Jasperien met haar pizza op de bank, ben ik je erg dankbaar dat je mij als onwetende in het medische veld op enthousiaste wijze onder je hoede hebt willen nemen. Ik waardeer het zeer dat ik altijd bij je terecht kon voor uitgebreide antwoorden op mijn vragen, ondanks dat je het de laatste tijd steeds drukker kreeg.

Jonie, jouw besluit om (deels) terug te gaan naar de praktijk bood mij de mogelijkheid om aan de slag te gaan met het CORE project. Ontzettend bedankt voor al het werk dat je verzet hebt, dit heeft mij een prachtige basis gegeven om mee verder te werken.
Jaap en Katrin, met jullie expertise is de kwaliteit van onze gezamenlijke artikelen enorm toegenomen. Veel dank daarvoor. Katrin, we hebben heel wat telefoontjes gepleegd en vele uurtjes met onze neuzen in de DHPCs doorgebracht, maar gelukkig was er ook tijd voor ontspanning. Laten we dat volhouden, we hebben nog lang niet alle high teas in de buurt uitgeprobeerd.
Menno, bedankt voor alle hulp bij de totstandkoming van de systematic review. Het heeft even geduurd, maar het heeft uiteindelijk een mooie publicatie opgeleverd.
Dear June Raine, thank you for you input on our article on the determinants of impact of DHPCs. I very much appreciated the opportunity to present the results of the CORE study at one of the Pharmacovigilance Working Party meetings at the EMA. It is very important to me to know that our efforts are taken so seriously.

De KNMP en NIV wil ik bedanken voor de ondersteuning van onze twee survey studies. Alle respondenten wil ik heel hartelijk bedanken voor de moeite die zij hebben willen nemen om onze vragenlijsten in te vullen. Zonder hen was het niet mogelijk geweest om concrete aanbevelingen te geven ter verbetering van de huidige risicocommunicatie van bijwerkingen van geneesmiddelen.
Veel dank ben ik verschuldigd aan: Annemieke, Marjolein, Annette, Steven, Mireille, Judith, Ellen, Wessel, Taco, Margje, Arna, Jaco, Fakhredin Tabatabaei, Ineke Crijns, Michelle en Jarno, die allen op praktische of adviserende wijze een onmisbare bijdrage hebben geleverd aan de CORE studie.
De aanwezigen bij alle meetings, de Klinische Farmacologie Monday Morning Meeting, het Gangoverleg en de M2o meeting (voormalig DruGs): bedankt voor jullie input naar aanleiding van mijn presentaties.
Mijn lidmaatschap van de PhD council heeft mij op een organisationeel niveau een kijkje in de onderzoeks-keuken geboden. Alle councilleden; bedankt voor de prettige samenwerking, en in het bijzonder Marijke tijdens de organisatie van de SHARE Spring Meeting.
Michelle, Mathijs, Ruth, Arna, Sieta, Liana Martirosyan, Valérie, Jasperien, Sara, Tobias, Jarno, Bas, Elisabeth, Francien, Liana Hakobyan, Grigory, Yan, Merel, Bauke, Misghina, Paul, Yunyu, Frank: bedankt voor alle hulp en gezelligheid. Valérie, ik heb bijzonder veel respect voor je. Hopelijk wordt al je werk beloond met een mooie publicatie. Wat we moeten vieren met taartjes natuurlijk.
Arna, mijn ‘partner in crime’ en vraagbaak. Dank voor het delen van je grote kennis van het veld en je vriendschap en gezelligheid tijdens alle tripjes die we samen hebben ondernomen, voornamelijk die naar IJsland. Kunnen we je nieuwe collega’s nog van wat muzikale educatie voorzien? Michelle, Sieta en Mathijs willen ons ongetwijfeld helpen.
Ruth, mijn werkzaamheden binnen de afdeling Klinische Farmacologie begonnen als stagiaire bij jou. Ik heb veel van je geleerd, maar nog veel meer waardeer ik onze vriendschap. Ik hoop dat we elkaar ook op creatief vlak blijven inspireren, ondanks de grotere afstand.

Mijn familie en vrienden hebben mij mede gevormd tot de persoon die ik nu ben. Moeke, Oma, ik hoop dat je tröts kinnen wezen veur twij. Ik haar Klaas en Opa der zo geern bie had tiedens mien permotie. Mijn vrienden en familie wil ik bedanken voor hun interesse en het aanhoren van alle ontwikkelingen gedurende mijn promotietraject.
Doran; uit het oog, maar zeer zeker niet uit het hart. Jij en Jean Paul ontzettend bedankt voor jullie hulp bij het maken van de cover van mijn proefschrift. Ik had me geen betere co-designer kunnen wensen.

Edwin en Marije, ik ben trots dat onze vriendschap al zo lang standhoudt. Gelukkig willen jullie bij gebrek aan een huwelijk genoegen nemen met het paranimf-schap. Alhoewel, promoveren is als trouwen in je eentje heb ik me laten vertellen. Ik kijk uit naar onze 30-jarige jubileum reis.

Rogier, mijn lief, mijn alles. Ik kan je niet genoeg bedanken voor alles en in het bijzonder je luisterend oor. Ook na bijna tien jaar prijs ik mijzelf nog steeds elke dag gelukkig met jou. Ik hoop dat we samen heel gelukkig oud worden.

Groningen, augustus 2013
Sigrid Piening

SHARE Publications

Research Institute for Health Research SHARE

This thesis is published within the **Research Institute SHARE** of the Graduate School of Medical Sciences (embedded in the University Medical Center Groningen / University of Groningen).
Further information regarding the institute and its research can be obtained from our internetsite: www.rug.nl/share.

More recent theses can be found in the list below.
((co-) supervisors are between brackets)

2013

Vu DH. *Clinical pharmacology of tuberculosis drugs and tuberculosis control in developing world; the involvement of private pharmacy and the individualization of treatment using dried blood spot*
(prof JRBJ Brouwers, prof DRA Uges, prof VH Le, prof DH Nguyen, dr JWC Alffenaar)

Sijtsma A. *Physical activity and overweight in young children*
(prof PJJ Sauer, prof RP Stolk, dr E Corpeleijn)

Rosicova K. *Regional mortality in Slovakia: socioeconomic indicators and ethnicity*
(prof JW Groothoff, dr JP van Dijk, dr A Madarasova-Geckova)

Bobakova D. *Youth subcultures and problem behaviours in Slovakia: hip-hop, techno-scene, metal, punk,skinheads and Roma*
(prof SA Reijneveld, dr JP van Dijk, dr A Madarasova-Geckova)

Arends I. *Prevention of recurrent sickness absence in workers with common mental disorders*
(prof JJL van der Klink, prof U Bültmann)

Theunissen MHC. *The early detection of psychosocial problems in children aged 0 to 6 years by Dutch preventive child healthcare; professionals and their tools*
(prof SA Reijneveld, dr AGC Vogels)

Bragaru M. *Sports and amputation*
(prof JHB Geertzen, prog PU Dijkstra, dr R Dekker)

Broesamle TC. *Designing health care services using systems thinking; a theory, a method and their application in the Dutch community pharmacy*
(prof JJ de Gier, prof JJ van der Werf)

Jong J de. *Antibiotics use in children; pharmacoepidemiological, practical and environmental perpectives in the Netherlands*
(prof LTW de Jong-van den Berg, dr TW de Vries)

Rettke HG & Geschwinder HM. *Long-term outcomes in stroke rehabilitation patients and informal caregivers*
(prof WJA van den Heuvel)

Fortington LV. *Enabling the elderly person with lower limb amputation through surgery, rehabilitation and long term care*
(prof JHB Geertzen, prof PU Dijkstra, dr GM Rommers)

Lako IM. *Depressive symptoms in patients with schizophrenia; count symptoms that count*
(prof K Taxis, prof D Wiersma)

Arnardottir AH. *Regulatory benefit-risk assessment; different perspectives*
(prof FM Haaijer-Ruskamp, prof PA de Graeff, dr PGM Mol, SMJM Straus)

Meijer A. *The forest trough the trees; investigating depression in patients with cancer and patients with myocardial infarction using systematic reviews and meta-analytic techniques*
(prof P de Jonge, dr HJ Conradi, dr BD Thombs)

Kuchenbecker WKH. *Obesity and female infertility*
(prof JA Land, prof BHR Wolffenbuttel, dr A Hoek, dr H Groen)

Rozenbaum MH. *Costs and effectiveness of extended vaccination strategies against pertussis and pneumococcal disease*
(prof MJ Postma, prof E Hak)

Kingma EM. *Intelligence and functional somatic symptoms and syndromes*
(prof JGM Rosmalen, prof J Ormel, prof P de Jonge)

Kedde JH. *Sexual health of people with disability and chronic illness*
(prof HBM van de Wiel, prof WCM Weijmar Schultz)

Horst PGJ ter. *Clinical pharmacology of antidepressants during pregnancy*
(prof B Wilffert, prof LTW de Jong-van den Berg)

Sinha R. *Adjustment to amputation and artificial limg, and quality of life in lower limb amputees*
(prof WJA van den Heuvel, prof P Arokiasamy, dr JP van Dijk)

2012

Pechlivanoglou P. *Applying and extending mixed-effects models in health in health economics and outcomes research*
(prof MP Postma, prof JE Wieringa, dr HH Le)

Verboom CE. *Depression and role functioning; their relation during adolescence and adulthood*
(prof J Ormel, prof WA Nolen, prof BWJH Penninx, dr JJ Sijtsema)

Benka J. *Living with rheumatoid arthritis: do personal and social resources make a difference?*
(prof JW Groothoff, prof JJL van der Klink, dr JP van Dijk, dr I Rajnicova-Nagyova)

Kalina O. *Sexual risky behaviour among Slovak adolescents and young adults; social and psychological factors*
(prof SA Reijneveld, dr JP van Dijk, dr A Madarasova-Geckova)

Crijns HJMJ. *Drug related safety issues affecting pregnancy outcome and concerning risk minimisation measures; emphasis on pregnancy prevention programmes*
(prof LTW de Jong-van den Berg, dr SMJM Straus)

Vries HJ de. *Working with pain; sustainable work participation of workers with chronic non-specific musculoskeletal pain*
(prof JHB Geertzen, prof JW Groothoff, prof MF Reneman, dr S Brouwer)

Karsten J. *On the threshold of disorder; definition and course of subthreshold depression and subthreshold anxiety*
(prof WA Nolen, prof BWJH Penninx, dr CA Hartman)

Abma FI. *Work functioning: development and evaluation of a measurement tool*
(prof JJL van der Klink, prof U Bültmann)

Rodrigues HCML. *Who's the patient? Ethics in and around maternal-fetal surgery*
(prof PP van den Berg, prof M. Düwell)

Munster JM. *Q fever during pregnancy; lessons from the Dutch epidemic*
(prof E Hak, prof JG Aarnoudse, dr ACAP Leenders)

Holwerda N. *Adaptation to cancer from an attachment theoretical perspective*
(prof R Sanderman, prof MAG Sprangers, dr G Pool)

Salonna F. *Health inequalities among Slovak adolescents over time*
(prof SA Reijneveld, prof JW Groothoff, dr JP van Dijk, dr A Madarasova-Geckova)

Kolarčik P. *Self-reported health and health risky behaviour of Roma adolescents in Slovakia*
(prof SAReijneveld, dr JP van Dijk, dr A Madarasova-Geckova)

Schreuder JAH. *Managing sickness absence; leadership and sickness absence behavior in hospital care*
(prof JW Groothoff, prof JJL van der Klink, dr CAM Roelen)

Hoen PW. *New perspectives on depression and heart disease*
(prof P de Jonge, prof J Denollet)

For more 2012 and earlier SHARE-theses see our website.